An Examination of the Known Economic Benefits of Physical Activity and its Practical Application in the Clinical Setting

A Dissertation
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

Zachary Todd Rourk

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
Doctor of Philosophy

Advisors: Eric M. Snyder, PhD
Michael G. Wade, PhD

May 2018

Copyright

Acknowledgements

I would like to thank my wife, Amanda. Her love, support and hard work are the reasons that I am able to live the life of my dreams. I thank my parents and my sister. Their wisdom and experience have been a safety net for me.

I would like to thank Dr. Eric Snyder and Dr. Michael Wade, without their help I would have slipped through the academic cracks many times over.

Lastly, I would like to thank the remainder of my committee, Dr. John Fitzgerald and Dr. Thomas Olson, both of whom have played an integral role in my academic journey.

Dedication

This dissertation is dedicated to my wife Amanda.

Amanda, I can tell you sincerely that if it weren't for you, I would not be where I am today. For a long time now, it has been my goal to earn a doctorate in Kinesiology. In part this goal has been a means to an end, to help better provide for our family. However, in part this goal has also been selfish, I simply love what I have been doing in school and have tried to continue for as long as possible. You are, unequivocally, the reason that I haven't been forced to stop.

Though my school related goals are long standing and important to me, my goal of having a family is significantly greater in age and importance. If forced to choose between one or the other I would have, without hesitation, chosen the latter. Because of you, I never had to make that choice.

The work that you have done and the sacrifices that you have made as a mother and a wife for our family is no less meaningful than what I have done in the classroom. No one else could have given me the freedom to pursue my goals the way that you have. As any happily married spouse should be, I am forever in your debt. I love you, and I thank you.

Table of Contents

List of Tables

List of Figures

Chapter 1.

Introduction

Introduction

It is well established that physical activity is an important factor related to health and well-being. Currently, the leading health institutions and associations, including the US Department of Health and Human Services (USDHHS), the American Heart Association (AHA), the American College of Sports Medicine (ACSM), the American Diabetes Association (ADA) and the American Cancer Society (ACS), recommend 150 minutes of moderate intensity, or 75 minutes of high intensity, physical activity per week (Colberg et al., 2010, 2016; Kushi et al., 2012). The current physical activity recommendations are based on a thorough body of evidence that demonstrates the positive effect of physical activity on a wide variety of health outcomes, including all-cause mortality, cardiovascular disease, stroke, type II diabetes mellitus, Alzheimer's disease, depression and breast and colon cancer (Aune, Norat, Leitzmann, Tonstad, & Vatten, 2015; Hamer & Chida, 2009; Johnson et al., 2013; Kyu et al., 2016; Lear et al., 2017; Sattelmair et al., 2011; Silveira et al., 2013; Wu, Zhang, & Kang, 2013). With this understanding in mind, it is surprising to find out that a majority of Americans fail to meet the recommendations for weekly physical activity (Troiano et al., 2008; Tucker, Welk, & Beyler, 2011; US Department of Health and Human Services, 2014).

The Exercise is Medicine® (EIM®) initiative, was developed in an effort to increase population physical activity through primary care practitioner action, in 2007. However, there is little evidence to suggest that it has been successful thus far. The general research question that this dissertation aims to address is, "how can the clinical Exercise is Medicine® model be integrated more effectively into the current medical system?

To answer this question, three studies were performed. First an updated economic analysis of the effects of physical inactivity on the US healthcare system was carried out in order to answer the question, “is it worth it to implement a physical activity intervention such as the EIM®?” It was hypothesized that the annual direct medical costs of physical inactivity would rival those of tobacco, and that the accomplishment of the Healthy People 2020 objective of increasing population physical activity levels by 10% would result in meaningful reductions in terms of caseload and direct medical costs. Second, a survey Assessment of Providers’ Knowledge and Understanding of the American College of Sports Medicine Exercise is Medicine® Initiative, was distributed to over 10,000 primary care practitioners in order to gain a better understanding of the current state of the EIM® strategy from the perspective of the primary care practitioner. It was hypothesized that primary care practitioners are not aware of the EIM® initiative, are not regularly implementing all of the steps of the EIM® process with their patient populations, do think that the steps of the EIM® process fall within their scope of practice and do believe that implementation of the EIM® initiative will increase population physical activity levels. Third, A Critical Evaluation of the Exercise is Medicine® Initiative with Proposed Amendments assesses each individual step of the EIM® process and the evidence on which it is based. From this assessment strengths and weaknesses of the process are highlighted and recommendations for improvement are made.

Chapter 2.

Review of Literature

Physical Activity Recommendations

Physical Activity, Physical Inactivity and Sedentary Behavior

Physical activity has been defined as any bodily movement that involves skeletal muscle and energy expenditure. Exercise is considered a subset classification of physical activity, in which the undertaken physical activity is purposeful, structured and repetitive (Caspersen et al., 1985; González, Fuentes, & Márquez, 2017).

Physical inactivity can be defined as a failure to accomplish the recommended weekly levels of physical activity, whereas, sedentary behavior is any behavior that requires less than or equal to 1.5 metabolic equivalents (González et al., 2017; Sedentary Behaviour Research Network, 2012). This dissertation focuses on the difference between physically active vs. physically inactive individuals, meaning the difference between those that do, and do not, accomplish the recommended weekly levels of physical activity. There is no commentary on levels of sedentary behavior accrued by either population.

Physical Activity Recommendations Past to Present

In 1995 the Centers for Disease Control and the American College of Sports Medicine issued a joint statement in which they recommended the accumulation of greater than 30 minutes of moderate or higher intensity activity on more than five days per week, based on observational and experimental studies that demonstrated positive health related outcomes given these exposures (Pate et al., 1995).

In 2007, the American College of Sports Medicine and the American Heart Association issued an updated recommendation for weekly exercise that included either five days per week of moderate exercise lasting 30 minutes or longer, or three days per week of vigorous intensity exercise lasting 20 minutes or longer, or a combination of moderate and vigorous exercise. These updates were made in an effort to clear up confusion as to how much of each, moderate and vigorous, activity was necessary for improved health (Haskell, Lee, Pate, Powell, & Blair, 2007).

The current physical activity recommendations from the US department of Health and Human Services are for 150 minutes of moderate intensity, or 75 minutes of high intensity physical activity per week (Physical Activity Guidelines Advisory Committee, 2008). Since this recommendation was made the American Heart Association, American College of Sports Medicine, American Diabetes Association and American Cancer Society have made updates to their recommendations to comply (American Heart Association, 2014; Colberg et al., 2016; Garber et al., 2011; Kushi et al., 2012). Recent evidence from the Prospective Urban Rural Epidemiology study suggests that failure to achieve these minimum weekly recommendations is associated with a 20-35% greater risk of all-cause mortality (Lear et al., 2017).

Estimates of Compliance

It is estimated that 56.5-90.4% of adult Americans do not meet the minimum weekly physical activity recommendations of 150 minutes of moderate, or 75 minutes of vigorous, physical activity per week (Troiano et al., 2008; Tucker et al., 2011). This wide range of estimates can be attributed to differences in methodological approaches (Troiano et al., 2008; Tucker et al., 2011). Tucker et al. (2011) found a discrepancy between self-reported data and data collected via 7-day continuous accelerometry. In this report, 62.0% of Americans met the weekly physical activity recommendations when asked to self-report, whereas only 9.6% of Americans met the recommendations according to accelerometry data. In an earlier report, Troiano et al. (2008) found similar discrepancies between self-report and accelerometry methods, and suggested that great care must be taken when interpreting self-reported physical activity data. However, the authors also suggested that the two methods give similar results regarding patterns of activity across gender and age groups. More recent accounts, based on self-reported data, suggest a pattern of increased physical activity amongst U.S. adults between 2008-2015. Specifically, the proportion of U.S. adults meeting weekly physical activity recommendations has increased from 43.5% in 2008, to 49.8% in 2015, with a peak level of 50% in 2012 (US Department of Health and Human Services, 2014). Regardless of methodology, these data suggest that much work needs to be done to increase population levels of physical activity.

Diseases Related to Physical Inactivity

There is currently an epidemic of diseases related to physical inactivity (Alzheimer's Association, 2015; Center for Behavioral Health Statistics and Quality, 2016; Mariotto, Yabroff, Shao, Feuer, & Brown, 2011; Mozaffarian et al., 2016b), with most studies indicating that the primary diseases related to a lack of adequate physical activity include cardiovascular disease (CVD), stroke, type II diabetes mellitus (T2DM), Alzheimer's disease (AD), depression, and breast and colon cancers. In the United States these diseases have high prevalence rates, are associated with high direct medical costs, are all currently ranked on the top ten list of causes of death in the United States, and have all been shown to be modifiable through physical activity intervention. Table 1 details this information and sources.

For these reasons, CVD, stroke, T2DM, AD, depression and breast and colon cancer were selected as a topic of further study within this dissertation. This group of diseases will be referred to as “the studied diseases” throughout this dissertation.

Physiological Adaptations to Aerobic Physical Activity

To better understand how physical activity intervention affects the relative risk of the studied diseases, it is important to have a good understanding of normal physiological adaptation to physical activity in healthy populations. The current recommendations for physical activity emphasize the use of aerobic methods and, not coincidentally, an overwhelming majority of the literature dedicated to the study of the effects of physical activity on disease have investigated aerobic methods of physical activity. For this reason, the focus of the, physiological adaptations to aerobic physical activity section and the mechanisms by which physical activity treats and prevents the studied diseases section, will be on aerobic physical activity.

The chief limiting factor related to aerobic physical activity performance is the supply of oxygen to working musculature. Many of the adaptations that occur as a result of participation in regular aerobic physical activity improve the rate at which oxygen is delivered to working muscle tissue. Maximal oxygen uptake (VO_2 max), is considered the gold standard in the assessment of the overall function and capacity of the aerobic system (Jones & Carter, 2000; Lavie et al., 2015; Rivera-brown & Frontera, 2012). Oxygen consumption can be described by the Fick Equation:

$$VO_2 = Q \text{ x } (CaO_2 - CVO_2)$$

Where VO_2 refers to oxygen consumption, Q refers to cardiac output, and CaO_2 - CVO_2 refers to the difference in oxygen saturation between arterial (Ca) and venous (CV) blood supply, commonly known as the arteriovenous oxygen difference (Rivera-brown & Frontera, 2012). Based on this equation it is possible to infer that oxygen consumption is primarily limited by the cardiovascular system, responsible for cardiac output, and the ability of working muscle to extract oxygen from the blood supply, quantified by the arteriovenous difference.

The Pulmonary System

Pulmonary Function can be described by the following equation:

$$\text{Minute Ventilation} = \text{Respiratory Rate X Tidal Volume}$$

Where minute ventilation is a measure of the volume of gas that enters and exits the lungs per minute, respiratory rate is the number of breaths per minute and tidal volume is the volume of air displaced per breath. During an acute aerobic physical activity bout, minute volume increases in a linear fashion relative to workload. Increases in tidal volume accomplish this response until ~65% of VO_2 max is reached, at which point, increases in respiratory rate are required to increase minute volume (Dempsey, 1985). Similarly, total pulmonary capillary blood volume increases with acute increases in workload and can reach levels three times that of resting values (Dempsey, 1985).

The main function of the pulmonary system during aerobic physical activity is to oxygenate pulmonary blood flow while extracting carbon dioxide, this occurs by way of diffusion at the alveoli-capillary interface. This process results in arterial oxygen saturation which informs the CaO_2 portion of the Fick equation. With the exception of elite level endurance athletes, or diseased individuals, arterial oxygen saturation is rarely reduced in response to aerobic physical activity and therefore, is not a limiting factor in aerobic physical activity performance (Mckenzie, 2012). In fact, the pulmonary system has been described as “overbuilt” for aerobic performance (Mckenzie, 2012) and, unlike the cardiovascular system, the pulmonary system is relatively non-adaptive to aerobic physical activity (Dempsey, 1985; Dempsey & Wagner, 1999; Mckenzie, 2012). This inflexibility may be a result of the acute ability of the pulmonary system to respond to the demands of physical activity, as minute ventilation has the capacity to increase 20-fold compared to resting levels (Mckenzie, 2012) and arterial oxygen saturation is only affected by physical activity of extreme intensity, within only the highest trained populations (Dempsey, 1985; Dempsey & Wagner, 1999; Powers et al., 1988; Richards, Mckenzie, Warburton, Road, & Sheel, 2004). There is limited evidence that aerobic physical activity improves the strength and endurance capabilities of respiratory muscles in healthy human populations, however these capabilities are not thought to be limiting to aerobic performance and improvements are miniscule in comparison to adaptations made by normal skeletal muscle in response to aerobic physical activity (Dempsey, 1985; Mckenzie, 2012).

The pulmonary system appears to be relatively non-adaptive to aerobic physical activity as it is rarely a limiting factor in aerobic performance.

The Cardiovascular System

The cardiovascular system can be described by the following equation:

$$Q = \text{Stroke Volume} \times \text{Heart Rate}$$

Where Q refers to cardiac output, stroke volume refers to the volume of blood pumped from the left ventricle per beat and heart rate is the number of times the heart beats per minute. During an acute bout of physical activity, cardiac output increases linearly with physical activity intensity from resting levels of ~5 L/min to exercising levels of, between 20 and 40 L/min; depending on the level of conditioning of the individual (Arena, Myers, & Guazzi, 2008; Rivera-brown & Frontera, 2012). Increases in cardiac output in response to physical activity are due to increases in stroke volume, until physical activity intensities of 40-60% of VO_2 max are reached, after which, Q is mediated by changes in heart rate (Gledhill, Cox, & Jamnik, 1994). Stroke volume at rest is typically ~50ml and can increase, based on the training status of the individual and intensity of physical activity to ~120 ml (Lavie et al., 2015; Rivera-brown & Frontera, 2012).

A primary short-term adaptation to aerobic physical activity is increased stroke volume, resulting from an increase in left ventricle muscle mass, dilation and contractility, collectively referred to as training induced cardiac remodeling (Baggish et al., 2008;

Lavie et al., 2015; Stuewe, Gwirtz, Agarwal, & Mallet, 2000). Increases in the volume and contractility of the left ventricle improve both the stroke volume and ejection fraction, the percentage of the blood volume in the left ventricle that is ejected each beat, resulting in a greater volume of blood flow per beat of the heart (Rivera-brown & Frontera, 2012). The increase in stroke volume leads to lower heart rates, both at rest, and at a given submaximal workload (Stuewe et al., 2000).

Another short-term adaptation to aerobic physical activity is a reduction in blood pressure. Currently there is debate as to whether or not post-exercise hypotension (Kenney & Seals, 1993) is an acute adaptation to physical activity or a short-term adaptation (Cornelissen, Buys, & Smart, 2013; Cornelissen & Fagard, 2005; Kelley, Kelley, & Tran, 2001; Thompson et al., 2001), as it has been observed in response to as little as one exposure to aerobic physical activity (Jennings et al., 1991; Meredith, Jennings, & Esler, 1990; Pescatello et al., 1999) and returns to baseline levels between 16 hours and 2 weeks post-exercise (Kenney & Seals, 1993; Meredith et al., 1990). Larger changes in post-exercise hypotension have been observed in hypertensive compared to normotensive populations (Cornelissen et al., 2013; Cornelissen & Fagard, 2005; Fagard & Cornelissen, 2007; Hagberg & Brown, 1995; Kenney & Seals, 1993). Specifically, a meta-analysis performed by Cornelissen & Fagard (2005) demonstrated a reduction of 2.4/1.6mmhg (SBP/DBP) in normotensive compared to a reduction of 6.9/4.9mmhg in hypertensive populations in response to chronic aerobic physical activity training interventions.

Along with changes in blood volume, aerobic physical activity leads to improved production of nitric oxide and endothelium-dependent vasodilation (Dawson, Green, Cable, & Thijssen, 1985; Goto et al., 2003; Maiorana, O'Driscoll, Taylor, & Green, 2003). Reduced viscosity, improved endothelium-dependent vasodilation and decreases in arterial stiffness lead to reductions in peripheral resistance, a mechanism of action for reduction in blood pressure (Paterson, Shephard, Cunningham, Jones, & Andrew, 1979; Shephard, 1992).

The cardiovascular system responds to aerobic physical activity primarily through training induced cardiac remodeling, resulting in a larger capacity to pump blood throughout the body. Secondarily, reductions in peripheral resistance and increases in blood volume result in reduced blood pressure, increased oxygen carrying capacity and more efficient delivery of oxygen to working musculature. These adaptations to aerobic physical activity occur in the short-term, as all of the adaptations discussed above begin shortly after the onset of a training program. However, prolonged training is necessary for the maintenance of such adaptations and leads to greater stability of achieved adaptations (Issurin, 2010). Long-term and stable adaptations related to aerobic physical activity by the cardiovascular system are imperative to the improvement and maintenance of overall health.

The Musculoskeletal System

Though improvements in aerobic physical activity performance are largely attributed to adaptations made at the cardiovascular level, significant adaptations are made in response to aerobic physical activity at the musculoskeletal level. Chief among these adaptations, are those related to improvements in oxygen diffusion rates, substrate uptake and storage, and oxidative metabolism.

Aerobic physical activity results in vascular remodeling at the myo-capillary level, referred to as angiogenesis (Risan, 1997), resulting in an increase in the number and density (per volume unit of muscle) of capillaries (Andersen & Henriksson, 1977; Holloszy, 2008; Ingjer, 1979; Laughlin & Roseguini, 2008; Rivera-brown & Frontera, 2012; Swift, Johannsen, Lavie, Earnest, & Church, 2017). This increase in capillarity improves the maximal muscle blood flow capacity (Jones & Carter, 2000), which can increase more than 30-fold compared to resting levels during maximal aerobic physical activity (Andersen & Saltin, 1985; Gibala et al., 1998). Increased capillarity also increases surface area, and mean local transit time, allowing for improved diffusion of oxygen and uptake of necessary substrates (Jones & Carter, 2000).

Along with increased muscular capillarization, the number and size of mitochondria, as well as the amount of oxidative and mitochondrial enzymes, are significantly elevated in response to aerobic physical activity; resulting in an increase in mitochondrial density and improved oxidative capacity of the affected muscle fibers (Egan & Zierath, 2012; Holloszy & Coyle, 1984; Howald, Hoppeler, Claassen, Mathieu, & Straub, 1985; Schantz, Sjoberg, & Svedenhag, 1986; Spina, Chi, & Hopkins, 1996; Suter, Hoppeler, & Claassen, 1995). This increase in mitochondrial density, particularly in the sub-sarcollemal region of the muscle fiber, reduces the diffusion distance of oxygen, leading to an increased rate of oxidative metabolism (Rivera-brown & Frontera, 2012). Increases in mitochondrial density have been observed after as few as eight to twelve weeks of training whereas increases in mitochondrial enzymatic activity, including citrate synthase, beta-hydroxyacyl-CoA dehydrogenase, mitochondrial thiolase, and carnitine acetyltransferase, were increased by 30% after only 7-10 days of training (Henriksson & Reitman, 1977; Klausen, Andersen, & Pelle, 1981; Spina et al., 1996). Reversal of the increase in mitochondrial density with the cessation of training was swift, occurring within six to eight weeks (Henriksson & Reitman, 1977; Klausen et al., 1981). However, individuals with longer training backgrounds (i.e. multiple years) appear to have developed more stable and long lasting adaptations (Holloszy & Coyle, 1984).

Mitochondria are the primary site in which oxidative metabolism occurs. An increase in mitochondrial density of the muscle cell is accompanied by concomitant increases in myoglobin, which is responsible for oxygen delivery within the cell, and malate-aspartate shuttles, which are responsible for transporting NADH across the mitochondrial inner membrane; importantly, NADH is a rate limiting enzyme of the krebs cycle and electron transport chain (Egan & Zierath, 2012; Harms & Hickson, 1983; Holloszy & Coyle, 1984; Schantz et al., 1986; Spina et al., 1996; Suter et al., 1995) . These adaptations are logical as an increased rate of oxidative metabolism during physical activity, facilitated by increased mitochondrial density, relies upon the increased availability of cellular stores of oxygen and increases the demand for NADH.

The respiratory exchange ratio (RER), a measure useful in the determination of the relative levels of β-oxidation and aerobic glycolysis, can be described by the following equation:

$$RER = VCO_2/VO_2$$

Where VCO_2 is the volume of carbon dioxide exhaled and VO_2 is the volume of oxygen inhaled. Aerobic training leads to a decrease in (RER) (Holloszy, 1973). Where a decrease in RER implies increased reliance upon β-oxidation relative to aerobic glycolysis, due to increases in muscle triglyceride stores and oxidative enzymes related to lipolysis and β-oxidation (Coggan, Kohrt, & Spina, 1990; Green, Jones, & Ball-Burnett, 1995; Green, Smith, & Murphy, 1990; Hurley, Nemeth, & Martin, 1986; Kiens & Essen-Gustavsson, B Christensen, 1993; Martin, Dalsky, & Hurley, 1993). These adaptations facilitate glycogen sparing, important in aerobic performance, as glycogen depletion has been associated with fatigue (Wagenmakers et al., 1991).

Relative to the musculoskeletal adaptations covered thus far, changes in muscle fiber type and size, tendon stiffness and bone density are long-term adaptations to chronic aerobic physical activity. It has been observed that aerobic physical activity preferentially increases the cross-sectional area of type-I muscle fibers through physical activity induced hypertrophy and causes a shift in fiber type from type IIx to type IIa, as well as type IIa to type I, but not from type IIx to type I (Andersen & Henriksson, 1977; Sale, MacDougall, & Jacobs, 1990; Simoneau, Lortie, & Boulay, 1985; Spina et al., 1996). In comparison to untrained populations, well trained endurance athletes have been shown to possess increased tendon strength of 20% (Kubo, Kanehisa, Kawakami, & Fukunaga, 2000). Similar cross sectional reports and research on animal species support the hypothesis that increased tendon strength is a long-term adaptation related to aerobic physical activity (Buchanan & Marsh, 2002; Kubo et al., 2000). Aerobic physical activity involving bone loading (i.e. running and walking) has been shown to have limited positive effects on bone density, with higher impact physical activities, including jumping and resistance training, recommended as the most effective means to improve bone density (Guadalupe-Grau, Fuentes, Guerra, & Calbet, 2009).

Short-term musculoskeletal adaptations to aerobic physical activity include increased capillary and mitochondrial density, increased reliance upon β-oxidation relative to aerobic glycolysis, and increases in proteins and enzymes related to the transport and metabolism of oxygen, NADH and triglycerides; including myoglobin and malate-aspartate shuttles. Long-term musculoskeletal adaptations include hypertrophy of type-I muscle fibers along with shifts in fiber type expression in the direction of type-I fibers. These adaptations reduce the demands placed on the cardiovascular system and lead to better overall health.

The Endocrine System

Increased vascular shear stress and hypoxic myocellular conditions, caused by aerobic physical activity, lead to upregulation of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), the primary regulator of nitric oxide (NO). VEGF and NO stimulate the production of endothelial progenitor cells (EPC's) that act on multiple pathways and facilitate improved angio- and arteriogenesis, vascular repair, reduced hypothalamic-pituitary-adrenal (HPA) axis action, increased production of antioxidants and improved neuro and synaptogenesis (Carmeliet, 2000; Lenk, Uhlemann, Schuler, & Adams, 2011; Stranahan, Lee, & Mattson, 2008; Shoshanna Vaynman, Ying,

& Gomez-pinilla, 2004). These adaptations are important to the treatment and prevention of multiple disease states, including cardiovascular disease, stroke, Alzheimer's disease, breast and colon cancer, and depression (Boer, Wörner, Verlaan, & Leeuwen, 2017; Lautenschlager, Cox, & Cyarto, 2012; Anne McTiernan, 2008; Schuler, Adams, & Goto, 2013; Wegner, Helmich, Machado, Nardi, & Arias-carrión, 2014)

Changes in myocellular ATP and Ca^+ caused by aerobic physical activity, result in the activation of the AMP-Activated Protein Kinase (AMPK) and the $Ca2^+$/Calmodulin-Dependent Protein Kinases (CaMKs) pathways, responsible for insulin independent translocation of the glucose transporter protein GLUT4. Increased translocation and levels of GLUT4 associated with aerobic physical activity are vital adaptations in the treatment of type II diabetes (Cheng & Kujala, 2012; Stanford & Goodyear, 2014). Chronic aerobic physical activity is also associated with decreased resting levels of leptin, the catecholamines adrenaline and noradrenaline, cortisol, insulin and thyroid hormones (McMurray & Hackney, 2005; Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008).

The endocrine response to aerobic physical activity is not fully understood, but it appears to be a primary system through which physical activity impacts disease states through improvement in endothelial and vascular function, regulation of insulin independent translocation of GLUT4 and maintenance of resting levels of a myriad of hormones.

Summary

The breadth of adaptations that occur at every level of the body, in response to physical activity, underpins the potential power of physical activity itself. In the next section, the mechanisms by which physical activity acts to treat the studied diseases will reinforce the concept, that physical activity has unprecedented capability and scope as a prescription, related to disease prevention and treatment.

Mechanisms by Which Physical Activity Treats and Prevents the Studied Diseases

Cardiovascular Disease and Stroke

The primary mechanism responsible for the prevention and treatment of CVD and stroke, related to physical activity intervention, appears to be the maintenance and restoration of endothelial function (Bowles & Laughlin, 2011; Lenk et al., 2011; Schuler et al., 2013). A promising mechanism for the treatment of those already suffering from various forms of CVD is the amplification of coronary collateral growth through physical activity intervention (Bowles & Laughlin, 2011; Heaps & Parker, 2011; Schuler et al., 2013; Seiler, 2003).

Endothelial Dysfunction

Endothelial dysfunction has been identified as a major contributor to CVD and stroke. Endothelial progenitor cells (EPC's) play an important, though not fully understood, role in endothelial function (Lenk et al., 2011). It is thought that EPC's reparative action at the endothelial wall level is related to either their ability to mature into endothelial cells themselves (Urbich & Dimmeler, 2004), or to signal for the secretion of growth differentiation factors, which in turn, stimulate mature endothelial cells to differentiate (Lenk et al., 2011). Circulating levels of EPC's appear to be regulated by NO concentrations which have been shown to be stimulated through aerobic physical activity in two ways (Adams et al., 2004; Laufs et al., 2004; Steiner et al., 2005). First, endothelial shear stress, associated with increased cardiac output, upregulates endothelial nitric oxide synthase (eNOS) (Fisslthaler, Dimmeler, Hermann, Busse, & Fleming, 2000; Newcomer, Thijssen, & Green, 2011), leading to increased levels of NO which, in turn, stimulate matrix metalloproteinase-9 (MMP-9) in bone marrow leading to the mobilization of EPC's (Iwakura et al., 2006). Second, hypoxia of the muscle cell during physical activity leads to increased levels of hypoxia-inducible factor-1 (HIF-1) which leads to increased production of vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1), and erythropoietin (EPO) (Asahara, Takahashi, & Masuda, 1999; Heeschen et al., 2003). In the same manner as NO, these three molecules stimulate the mobilization of EPC's via MMP-9 in the bone marrow. Aerobic physical activity has also been shown to stimulate the chemokine receptor type 4 (CXCR4) and the very late antigen-4 VLA4 receptors, responsible for the "homing" of EPC's to damaged sites along the endothelium (Askari et al., 2003; Lenk et al., 2011).

Coronary Collateral Growth

Atherosclerosis, the hardening and narrowing of blood vessels, especially the arteries, is one of the most common underlying causes of CVD (Mozaffarian et al., 2016a). In response to atherosclerotic conditions, including ischemic conditions and vascular shear force, the vasculature system may develop alternative arterial and capillary pathways, via arteriogenesis and angiogenesis, in an effort to supply oxygen to the heart (Heil, Eitenmuller, Schmitz-Rixen, & Schaper, 2006; Risan, 1997). This process, termed coronary collateral growth, has been shown to reduce the magnitude of infarct and lead to improved chances of survival (Heaps & Parker, 2011). Newly formed arteries are referred to as “natural bypasses” and are viewed as possible alternatives to invasive bypass surgeries and angioplasty (Heil et al., 2006; Seiler, 2003). Though the exact underlying mechanisms of angiogenesis and arteriogenesis are not fully understood, it appears that many of the key molecules involved in healthy endothelial function play important roles, including eNOS, VEGF, HIF-1, SDF-1, CXCR4 and EPC’s (Carmeliet, 2000; Heil et al., 2006; Schuler et al., 2013; Seiler, 2003). The role of these molecules along with the role of shear stress as a mediating factor in arteriogenesis have led researchers to hypothesize that physical activity may serve as a stimulating intervention, due to the fact that exercise is known to stimulate these pathways (Carmeliet, 2000; Heil et al., 2006; Schuler et al., 2013; Seiler, 2003). There is strong evidence to support this theory in animal models, however results of human interventions are less clear (Heaps & Parker, 2011; Seiler, 2003). Researchers have theorized that the current assessment techniques available for use in human trials are not sensitive enough to capture collateral growth, a problem not faced in animal trials (Heil et al., 2006; Seiler, 2003).

Type II Diabetes Mellitus

There are multiple mechanisms by which physical activity improves symptoms of T2DM, the most crucial of which appears to be the improved translocation, and abundance of, glucose transporter proteins. Other mechanisms include maintenance, and increases in, muscle mass, reductions in visceral fat deposits, improvements in mitochondrial function, and improvements in musculoskeletal glycogen synthesis.

Translocation and Abundance of Glucose Transporter Proteins

Type II Diabetes Mellitus, is the result of the development of insulin resistance at the muscle, liver and adipose tissue levels (DeFronzo & Tripathy, 2009; Stanford & Goodyear, 2014). Resistance to insulin leads to the inability of these sites to uptake glucose from the blood, this inability primarily stems from the inability of insulin to stimulate the translocation of glucose transporter proteins, specifically GLUT4 (Burr, Rowan, Jamnik, & Riddell, 2010; Cheng & Kujala, 2012; Stanford & Goodyear, 2014; Strasser & Pesta, 2013). It has been demonstrated that acute and chronic physical activity bouts, both aerobic and resistance training based, increase blood glucose uptake through increased abundance and translocation of GLUT4, via pathways alternative to the insulin dependent pathway (Gaster, Vach, Beck-Nielsen, & Schroder, 2002; Higashida, Kim, Higuchi, Holloszy, & Han, 2011; Holten et al., 2004; Richter & Hargreaves, 2013). It appears that changes in cellular AMP, ATP and $Ca2^+$ caused by muscular contraction during physical activity, result in multiple signaling cascades that result in the translocation of GLUT4 (Richter & Hargreaves, 2013; Rockl, Witczak, & Goodyear, 2008; Stanford & Goodyear, 2014). These pathways are not fully understood, however, Stanford & Goodyear (2014) referred to the AMP-Activated Protein Kinase (AMPK) and the $Ca2^+$/Calmodulin-Dependent Protein Kinases (CaMKs) as the most studied and influential pathways. It is recognized that insulin dependent, AMPK and CaMKs share common downstream targets; the molecules AS160 and TBC1D1, both of which play an integral role in the translocation of GLUT4 (Stanford & Goodyear, 2014). This common pathway may be a key factor in the long term positive effects of physical activity on insulin sensitivity.

Other Mechanisms

Skeletal muscle typically constitutes more than one third of total body mass and is the largest site of blood glucose uptake in the body (Strasser & Pesta, 2013). Increases in muscle mass, through resistance training, are proposed to increase the potential for blood glucose uptake and reverse the age-related effects of sarcopenia (Gaster et al., 2002). It has been observed that type I muscle fibers have greater insulin sensitivity and are typically expressed in lower relative amounts in diabetic populations (Albright, Franz, & Hornsby, 2000; Corcoran, Lamon-Fava, & Fielding, 2007). Fiber type shifts, towards type I (those that are more oxidative in nature) as a result of aerobic training, are considered beneficial adaptations.

Increased visceral fat deposits are associated with increased risk of T2DM (Bjorntop, 1991; Coggan et al., 1990; Ivy, 1997), possibly due to the suppressant effect of tumor necrosis factor-α (TNF-α), a hormone like substance produced in adipose tissue, on GLUT4 translocation (Stephens & Pekala, 1991). Aerobic and resistance training have been shown to reduce visceral fatty deposits, preferentially (Despres, Nadeau, & Bouchard, 1988).

Populations suffering from T2DM have been shown to have reduced function and abundance of mitochondria, which has been linked to insulin resistance (Patti et al., 2003). Aerobic physical activity has been shown to completely reverse these deficits (Meex et al., 2010).

Once blood glucose is transported into the cell it is either metabolized or converted to glycogen via the enzyme glycogen synthase. Populations with T2DM have been observed to have low levels of glycogen synthase (Shulman et al., 1990), these levels can be improved through aerobic and resistance training interventions (Cauza, Hanusch-Enserer, & Strasser, 2005; Ferrara, Goldberg, Ortmeyer, & Ryan, 2006; Hughes, Fiatarone, & Fielding, 1993). Based on this abundant evidence, it is likely that physical activity reduces T2DM primarily through increased translocation and abundance of GLUT4, as well as through peripheral muscular adaptations including increased mitochondrial function, density and number.

Alzheimer's Disease

The primary mechanisms by which physical activity is believed to prevent and slow the rate of decline in AD appear to be related to improvements in cerebral blood flow, reduction in oxidative stress and improvements in neuronal plasticity (Chen, Zhang, & Huang, 2016; Lange-asschenfeldt & Kojda, 2008; Radak et al., 2010).

Cerebral Blood Flow

AD is associated with reduced cerebral blood flow, caused in part by limited functional angiogenesis and arteriogenesis, characteristics of overall impaired endothelial function, similar to that of CVD (Torre, 2002). Due to these similarities, the role that physical activity plays in the treatment and prevention of AD is comparable to its role in the treatment and prevention of CVD. Specifically, increases in vascular shear stress and hypoxic conditions, induced by physical activity, lead to increased production of eNOS and HIF-1 which lead to increased production of NO and VEGF, respectively. NO and VEGF stimulate MMP-9 in bone marrow, which causes an increase in circulating EPC's. These EPC's are responsible for a myriad of endothelial functions related to vascular plasticity, including endothelial repair and an increase in functional capacity for angio- and arteriogenesis (Lenk et al., 2011). Increases in the rate of angiogenesis lead to increased cerebral capillarization and cerebral blood flow, adaptations thought to play a major role in the prevention and treatment of symptoms of AD (Lange-asschenfeldt & Kojda, 2008).

Reduction of Oxidative Stress

AD is characterized by cerebral amyloid angiopathy (CAA), or high levels of extracellular senile plaque, comprised primarily of amyloid-β (Aβ) as well as the buildup of intracellular neurofibrillary tangles, comprised of the protein tau (Dubois et al., 2010). Aβ accumulation reduces cerebral blood flow through its physical presence within cerebral vasculature and inhibits the activity of eNOS (Suhara et al., 2003). Measured accumulation of these proteins is a diagnostic characteristic of AD (Ahlskog, Geda, Graff-radford, & Petersen, 2011). Aβ and tau are also associated with increased production and accumulation of reactive oxygen species (ROS) which in turn lead to high levels of oxidative stress, causing neurodegeneration and increased CAA, creating a damaging cycle of increased Aβ production (Zhao & Zhao, 2013).

Moderate and high intensity aerobic physical activity have been shown to both reduce the production capacity for ROS and increase the production of antioxidants including eNOS, brain-derived neurotrophic factor (BDNF), and VEGF. These positive adaptations to physical activity have been observed to lead to reductions in the concentration of Aβ plaques, neurofibrillary tangles of tau and overall markers of oxidative stress (Chen et al., 2016; Lange-asschenfeldt & Kojda, 2008; Radak et al., 2010; Shoshanna Vaynman et al., 2004).

Neuronal Plasticity

Neuronal plasticity refers to the ability of the brain to make new neurons and synapses through the processes of neurogenesis and synaptogenesis, respectively. These processes are integral to the regulation of learning and the formation of long-term memory. Patients suffering from AD have decreased capacity for both processes (Shoshanna Vaynman et al., 2004).

An important neurotrophin that mediates neurogenesis and synaptogenesis is BDNF (Shoshanna Vaynman et al., 2004). It has been observed, in experimental trials, that BDNF gene deletion or inhibition leads to decreases in long term potentiation, the process by which learning and memory formation take place (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996; Kang, Welcher, Shelton, & Schuman, 1997). Further, these deleterious effects can be reversed with the application of external sources of BDNF or overexpression of the gene (Korte et al., 1995; Patterson et al., 1996). The mechanism(s) by which BDNF regulates neurogenesis, synaptogenesis, memory and learning are not fully understood, however, it has been observed that BDNF regulates the production of cAMP response-element-binding (CREB) protein, a transcriptional factor that plays an integral role in the formation and survival of neurons, and synapsin I (SYN-I), a phosphoprotein integral in the formation and survival of synapses (Gomez-Pinilla, So, & Kesslak, 2001; S. Vaynman, Ying, & Gomez-Pinilla, 2003).

Cellular hypoxia, caused by physical activity, leads to the production of HIF-1, which in turn stimulates the production of the circulating factors VEGF, SDF-1 and EPO (Lenk et al., 2011). Although this same cascade is important to endothelial function in both CVD and AD due to the downstream production of EPC’s and the corresponding increase in arterio- and angiogenesis, special attention has been paid to VEGF as a primary regulator of brain-derived neurotrophic factor (BDNF) (Vaynman & Gomez-Pinilla, 2006). It has been demonstrated that circulating BDNF and amount of physical activity performed are positively correlated and that these increased levels of circulating BDNF, post- physical activity, have been positively correlated with levels of CREB and SYN-I (Shoshanna Vaynman et al., 2004). CREB and SYN-I are responsible for stimulating neuro- and synaptogenesis (Matta, Cevada, & Monteiro-junior, 2013).

Physical activity is thought to reduce the risk of, and ameliorate the symptoms of AD, at least in part, through the stimulation of BDNF and the concomitant improvements in neuro- and synaptogenesis, the underpinning mechanisms for learning and long-term memory formation.

Depression

There are two main mechanisms by which physical activity is thought to effect depression; adaptation of the hypothalamic-pituitary-adrenal (HPA) axis and the neurotrophic hypothesis (Matta et al., 2013; Wegner et al., 2014).

Hypothalamic-Pituitary-Adrenal Axis

Depression is thought to be caused, in part, by dysfunctional control of cortisol levels through the HPA-axis. Stress leads to a release of corticotropin-releasing hormone (CRH) in the hypothalamus that stimulates the pituitary to release adrenocorticotropic hormone, which in turn, stimulates the adrenal gland to release cortisol, “the stress hormone”, which acts upon mineralocorticoid receptors (MR) throughout the body (Matta et al., 2013). Too much cortisol-MR interaction in the brain can lead to neuronal injury pathways supposed to cause depression (Yuan et al., 2015). Although acute bouts of physical activity are known to stimulate this system and lead to the release of cortisol, chronic aerobic physical activity has been shown to reduce resting cortisol levels and the level of cortisol increase in response to stressful stimuli (Matta 105). The exact mechanism by which physical activity effects the HPA axis is unknown, however it is thought that physical activity may improve the density and sensitivity of MR and inhibit cortisol synthesis, leading to a net effect of improved cortisol sensitivity (Matta et al., 2013).

The Neurotrophic Hypothesis

Depression is characterized by decreased hippocampal volume as a result of decreased neuro- and synaptogenesis (Wegner et al., 2014). The hippocampus is the center of learning, memory formation (discussed in the AD section) and mood state or emotion. physical activity increases hippocampal volume by increasing neuronal plasticity, neuro- and synaptogenesis in the same manner described in the AD section above (Matta et al., 2013; Wegner et al., 2014). Muscular contraction and hypoxic conditions lead to increased production of neurotrophins, including BDNF and VEGF, which lead to increased production of CREB and SYN-I, that in turn, stimulate neuro- and synaptogenesis. These adaptations cause increased hippocampal volume leading to improved symptoms of depression (Rebar, Stanton, Geard, Short, & Duncan, 2015).

Breast and Colon Cancer

The strongest evidence for a protective role played by physical activity against cancer is related to breast cancer. Relatively little is known about the mechanisms of action related specifically to colon cancer, as mush less research has been done in this area. It is early in the research process and the mechanisms studied are currently considered hypotheses, as enough evidence has not yet been gathered. Proposed mechanisms by which physical activity treats and prevents breast, colon and other cancers, include reduction in sex hormone levels, improvement of insulin sensitivity, altered adipocytokines, decreased inflammation and improved immune function (Boer et al., 2017; Graf & Wessely, 2010; Anne McTiernan, 2008).

Reduction in Sex Hormones

Free circulating estrogen is associated with increased risk for breast cancer (Key, Appleby, Barnes, & Reeves, 2002). Moderate intensity aerobic physical activity is associated with decreased production of estrogen, whereas reduction in adipose tissue, physical activity induced or not, results in the increased production of sex hormone-binding globulin (SHBG) (A McTiernan et al., 2004), a steroid binding glycoprotein that regulates the availability of free circulating estrogen (Gascon, Valle, & Martos, 2000). Combined, these adaptations lead to a net reduction in free circulating estrogen, especially in post-menopausal females, a possible protective effect of physical activity (M. F. Chan, 2007; Mctiernan, 2006; Verkasalo, Thomas, Appleby, Davey, & Key, 2001).

Improvement of Insulin Sensitivity

Insulin resistance has also been associated with increased risk of cancer. High levels of insulin due to reduced insulin sensitivity can result in tumor development directly, by reducing apoptosis and increasing cell proliferation, or indirectly, by reducing production of SHBG (Kaaks & Lukanova, 2001). The effect of physical activity on insulin resistance has been discussed in the T2DM section above.

Altered Adipocytokines

Leptin is a hormone produced in adipose tissue that regulates cell growth and proliferation and has been observed to be overexpressed in breast tumors (Harris, Tworoger, Hankinson, Rosner, & Michels, 2011; Jarde, Caldefie-Chezet, & Goncalves-Mendes, 2009). Adiponectin is an anti-inflammatory hormone, inversely related to fat mass, that acts to reduce proliferation of breast cancer cells, downregulate TNFα and serves as an indicator of insulin sensitivity (Grossmann, Ray, & Nkhata, 2010; Jarde et al., 2009; Tworoger, Eliassen, & Kelesidis, 2007). There is evidence to suggest that the ratio of leptin to adiponectin is an important factor in breast cancer prevention (Grossmann et al., 2010). Both aerobic and resistance training have been shown to lower leptin levels and raise adiponectin levels, creating a more favorable ratio (Bouassida et al., 2010; de Salles, Simao, Fleck, Dias, & Kraemer-Aguiar, LG Bouskela, 2010; Gleeson et al., 2011). These adaptations are achieved through three mechanisms; reduction in adipose tissue, increases in anti-inflammatory cytokines due to muscular contraction, and reduction in Toll-like receptors on macrophages and monocytes (Gleeson et al., 2011).

Decreased Inflammation

C-reactive protein (CRP), interleukin 6 (IL-6) and TNFα are all inflammatory factors that have been associated with increased cancer risk (Il'yasova, 2005). Exercise has been shown to suppress the expression of TNFα and reduce the presence of inflammatory markers in the body (Petersen & Pedersen, 2005) . The exact mechanism by which these factors are downregulated is not known, however it has been shown that increased levels of adiponectin and decreased fat mass play an important role (Anne McTiernan, 2008).

Improved Immune Function

Natural killer (NK) and cytotoxic T cells (T-cells) are thought to play integral roles in the immune systems defensive role against cancer (Anne McTiernan, 2008). During aerobic physical activity catecholamine release leads to increases in NK cells and T-cells of 150-300 and 50-100 percent respectively (Nieman, 1994). Upon the release of cortisol, shortly after physical activity, NK and T-Cell levels drop to levels below baseline, but there is evidence to suggest that they may be functioning at higher capacity, offsetting the drop below baseline (Nieman, 1994). There is not enough evidence at this point to draw any conclusions as to how physical activity affects the immune system and how those effects may relate to breast or colon cancer risk, however the hypothesis remains (Graf & Wessely, 2010; Anne McTiernan, 2008; Pedersen & Hoffman-Goetz, 2000).

Summary

The mechanisms of action by which physical activity acts upon the studied disease states are widely variable. Physical activity is the initial stressor for many adaptive responses that aid the human body in warding off disease. This multi-variable protective effect cannot be oversold, as it has the potential to replace multiple pharmacological interventions, for multiple and concurrent disease states, in a single prescription.

Physical Activity vs. Pharmacological Intervention

Physical activity has been shown to be just as, if not more, effective than pharmacological intervention in treating the studied diseases (Alberti, Zimmet, & Shaw, 2007; Aune et al., 2015; Blondell, Hammersley-mather, & Veerman, 2014; Cole et al., 2009; Diep, Kwagyan, Kurantsin-Mills, Weir, & Jayam-Trouth, 2010; Diniz, Pinto, Guimares, Gattaz, & Forlenza, 2009; Freedman et al., 2011; Hamer & Chida, 2009; Jeon, Hu, Lokken, Dam, & M., 2007; Johnson et al., 2013; Kyu et al., 2016; Law, Morris, & Wald, 2009; Li, Loerbroks, & Angerer, 2013; Li & Siegrist, 2012; Naci & Ioannidis, 2013; Robsahm et al., 2013; Sattelmair et al., 2011; Silveira et al., 2013; Francesco Sofi, Capalbo, Cesari, Abbate, & Franco, 2008; Wegner et al., 2014; Wolin, Yan, Colditz, & Lee, 2009; Wu et al., 2013). Table 2 provides a summary of the relative risk for each disease studied, given both physical activity and pharmacological intervention. Physical activity has the added advantage of working to treat all of the diseases related to physical inactivity at once, with minimal potential for drug interactions or adverse side effects.

This section will compare the protective effects of physical activity as a preventive measure to pseudo-preventative pharmacological interventions, for each of the studied diseases. The qualifier “pseudo-preventative” is used to underline the fact that there are no true preventative pharmacological interventions for any of the disease states in question. Instead prescription medications are used only in high risk populations, or with those already afflicted by disease, due to the potential for adverse side effects.

Cardiovascular Disease and Stroke

In the past decade, there have been four meta-analyses that have analyzed the role of physical activity in preventing heart disease (Li et al., 2013; Li & Siegrist, 2012; Sattelmair et al., 2011; Francesco Sofi et al., 2008). Similarly, there have been four meta-analyses that have analyzed the role of physical activity in preventing stroke (Diep et al., 2010; Kyu et al., 2016; Li et al., 2013; Li & Siegrist, 2012). These analyses share the same conclusion, moderate to high levels of physical activity reduce the risk of heart disease and stroke by 14-34% and 11-29% respectively. There is also evidence, though less definitive in the case of stroke, for a dose-response relationship between physical activity and its protective effects.

In a meta-analysis of 154 RCT’s of blood pressure lowering drugs, including beta-blockers, for the prevention of heart disease, it was found that the protective effect of blood pressure medication was directly due to reduction in blood pressure. The combined effect for all drug types was a reduction in risk of CVD by 15% and of stroke by 27% (Law et al., 2009). This study highlights the similar reduction in risk between physical activity and pharmacological intervention. Reduction in risk was given for all medications combined, due to the fact that no drug showed favorable outcomes compared to another, a phenomenon that has been well documented (Blood Pressure Lowering Treatment Trialists' Collaboration, 2003, 2008; Law et al., 2009).

Type II Diabetes Mellitus

In the past decade, two meta-analyses have been performed detailing the relative risk of developing T2DM with and without physical activity.

A meta-analysis of 81 studies found that those in high physical activity groups, compared to low physical activity groups, were 35% (RR- 0.65, 95% CI 0.59–0.71) less likely to develop T2DM (Aune et al., 2015). The authors looked more specifically at different intensities and types of physical activity including leisure time activity, vigorous activity, moderate activity, light activity, resistance training and walking and reported that all investigated physical activity categories were associated with 25-40% reductions in risk of T2DM with the exceptions of walking, occupational activity and cardiorespiratory fitness associated with 15%, 15% and 55% reductions in risk, respectively. Aune et al. (2015) concluded that increased levels of physical activity, of any kind, are beneficial in reducing the risk of T2DM.

Jeon, Hu, Lokken, Dam, & M. (2007) conducted a meta-analysis of 10 prospective cohort studies of the effects of moderate physical activity on T2DM outcomes and reported that regular participation in physical activity of moderate intensity was associated with a 31% (RR-0.69, 95% CI 0.58–0.83) lower risk of developing T2DM compared with being physically inactive. The authors also found that participants that walked briskly for more than two and a half hours per week were 30% less likely, compared to those that took part in little to no walking, to develop T2DM (RR-0.70 95% CI 0.58–0.84).

According to the most recent standards of medical care in diabetes from the American Diabetes Association, Metformin is the only recommended drug for use in the treatment of T2DM, based on strong evidence in terms of efficacy and long-term safety. Per the same report, Metformin is less effective overall than lifestyle intervention strategies, that include diet and physical activity interventions, and equally effective in populations with a BMI >35. This same report goes on to address the use of other drugs with the following statement, “For other drugs, cost, side effects, and lack of a persistent effect require consideration” (American Diabetes Association, 2014).

In a summary of major diabetes intervention studies Alberti, Zimmet, & Shaw (2007) found that drug interventions involving Metformin, Troglitazone, Acarbose, Orlistat, and Rosiglitazone showed risk reductions ranging from 25-75% whereas lifestyle interventions showed risk reductions ranging from 28-67%. Similarly, in a systematic review and meta-analysis of pharmacological and lifestyle interventions, lifestyle interventions were found to be at least as effective as pharmacological interventions (Gillies et al., 2007). Supporting this sentiment, Naci & Loannidis, (2013) concluded that physical activity is equally as effective as drug intervention in terms of mortality caused by T2DM. Furthermore, Montori & Fernandez-Balsells (2009) concluded that there is not enough evidence to support the current widespread use of medications to treat T2DM.

Besides failing to be more effective than physical activity T2DM medications are associated with side effects that include gastrointestinal distress, decreased liver function, increased risk of congestive heart failure and increase risk of bone fracture (Gillies et al., 2007; Lago, Singh, & Nesto, 2007; Loke, Singh, & Furberg, 2009; Nissen & Wolski, 2007, 2010), and are only recommended for individuals at high risk (American Diabetes Association, 2014).

Alzheimer's Disease

Over the past decade three meta-analyses have investigated the role of physical activity as a preventative factor for dementia, in previously non-demented populations (Blondell et al., 2014; Hamer & Chida, 2009; F Sofi et al., 2010).

In a meta-analysis that included 47 cohorts, Blondell et al. (2014) found that participants with higher levels of activity, compared to those with lower levels of activity, were 35% less likely to develop cognitive decline (RR- 0.65, 95% CI 0.55-0.76), an early indicator of dementia, and 14% less likely to develop dementia (RR- 0.86, 95% CI 0.76-0.97), the disease category under which AD falls.

Similarly, in a meta-analysis of 15 prospective studies, Sofi et al. (2010) found that participants in the high activity group compared to those in a physically inactive group were 38% less likely to develop cognitive decline (HR 0.62, 95% CI 0.54–0.70) and participants in a low-moderate activity group were 35% less likely to develop cognitive decline (HR 0.65, 95% CI 0.57–0.75).

Lastly, in a meta-analysis of 16 prospective studies, Hamer and Chida (2009) found that participants in the highest, compared to the lowest, activity level group had a 28% lower chance (RR- 0.72 95% CI 0.60–0.86) of developing dementia and a 45% lower chance (RR- 0.55 95% CI 0.36–0.84) of developing AD, specifically.

In a more recent retrospective study, Tolppanen et al. (2015) found that physical activity during mid-life, decreased the relative risk of AD and dementia later in life. Furthermore, the maintenance of, or increase in activity, past the mid-life point also led to a reduction in risk of AD and dementia later in life.

An important limitation to these conclusions is the lack of sufficient evidence to prove a causal relationship; that is to say, all three sets of authors discussed the possibility that dementia may in fact be the reason that participants do not participate in physical activity (Blondell et al., 2014; Hamer & Chida, 2009; F Sofi et al., 2010).

There are no pharmacological interventions that have been used to effectively treat AD. Pharmacological interventions used to slow cognitive decline and other symptoms related to AD utilize cholinesterase inhibitors (CI's). This group of medication is recommended only for use in populations with moderate to severe forms of AD (Vahabzadeh, Delaffon, & Abbas, 2010) due to side effects, including nausea, vomiting, diarrhea, dizziness, headache, weight loss, anorexia, muscle cramps, abdominal pain (Geldmacher, 2003) and a limited magnitude of effect (Vahabzadeh et al., 2010). In a meta-analysis of four RCT's of CI's used to prevent the progression of mild cognitive impairment to AD, CI's were found to reduce the risk of further progression by 25% (RR- 0.75 95% CI 0.65-0.87) (Diniz et al., 2009).

Depression

Research related to physical activity as a preventative strategy for depression is limited. Instead, researchers focus on physical activity as a means of treatment.

In a meta-analysis of 10 longitudinal trials, Silveira et al. (2013) reported a 0.61 (95% CI: –0.88 to –0.33) standard deviation reduction in the intervention group compared to the control group. In the same analysis, it was reported that physical activity intervention groups were 49% (RR- 1.49; 95% CI 1.10–2.03) more likely to see improvements in symptoms of depression compared to controls.

Currently, the area of research related to the efficacy of pharmacological intervention and physical activity intervention as treatments for depression is contentious. In a summary of seven meta-analysis regarding the efficacy of physical activity as a treatment, Josefsson, Lindwall, & Archer (2014) stated that "the main results from seven meta-analyses so far show that physical activity has an antidepressant effect compared with control conditions that ranges from slightly moderate (g = –0.40) to very large (g = –1.39). However, the majority of the included studies in all these meta-analyses suffer more or less from serious methodological problems (e.g., small samples, inadequate allocation concealment, lack of intention-to-treat analysis and blinding, and lack of clinical interviews to diagnose depression)".

Similarly, the efficacy of anti-depressant medication is under scrutiny as some researchers claim that drug-placebo differences are relatively small for depressed patients (Kirsch et al., 2008), whereas others claim that the drug effect is large and always present

(Fountoulakis & Moller, 2011). Interestingly both groups of researchers used the exact same data set when coming to these contradictory conclusions.

In favor of physical activity and antidepressant use, Blumenthal et al. (2007), after conducting a prospective cohort trial, concluded that physical activity and drug interventions were equally effective, and both were more effective than placebo.

Breast Cancer

In the past decade, there has been one meta-analysis performed, specifically analyzing the role of physical activity in the prevention of breast cancer. Wu et al. (2013) analyzed 31 prospective studies with 63,786 participants and reported that, overall, participation in physical activity reduces the risk of breast cancer by 12% (RR-0.88 95% CI- 0.85–0.91). The authors also reported a dose-response relationship between physical activity and risk of breast cancer, stating that the risk of breast cancer decreased by five percent for every two hour/week increase in moderate to vigorous physical activity.

Tamoxifen and Raloxifene are the two pharmacological options recommended by the Breast Cancer and Environmental Research Coordinating Committee, to reduce the risk of breast cancer in high risk populations (Interagency Breast Cancer and Environmental Research Coordinating Committee, 2013). Though Tamoxifen has been shown to reduce breast cancer risk by 24% (RR-1.24, 95% CI 1.05–1.47) (Freedman et al., 2011) and Raloxifene has been shown to be 76% as effective as Tamoxifen (Freedman et al., 2011; Vogel et al., 2010), both are recommended for use only in high risk populations due to toxic side effects that include increased risk of endometrial cancer, stroke, pulmonary embolism, deep vein thrombosis, and cataracts (Fisher et al., 1998; Freedman et al., 2011; Vogel et al., 2010).

Colon Cancer

Three meta-analyses have been performed analyzing the role of physical activity in the prevention of colorectal cancer (Johnson et al., 2013; Robsahm et al., 2013; Wolin et al., 2009). In a meta-analysis of colorectal cancer by anatomical region, Robsahm et al. (2013) found a reduction in risk of proximal and distal colon cancer of 24% (RR 0.76, 95% CI 0.70-0.83) and 23% (RR 0.77, 95% CI 0.71–0.83) respectively, but did not find a significant reduction in rectum cancer. Johnson et al. (2013) found an overall reduction in the risk of colorectal cancer of 12% (RR-0.88, 0.86–0.91). Subgroup analysis revealed a 27% (RR- 0.73, 0.68–0.79) reduction in colon cancer, and a non-significant relationship for rectum cancers. Wolin et al. (2009) conducted a meta-analysis in which physical activity was found to reduce the risk of overall colorectal cancer by 24% (RR-0.76 95% CI- 0.72, 0.81). Taken together, these studies lend evidence to the theory that physical activity may be effective in preventing colon, but not rectum cancer.

Relatively high doses of aspirin and Cox-2 selective inhibitors are the current pharmacological interventions directed at preventing colorectal cancer (A. T. Chan & Giovannucci, 2010). Cole et al. (2009) performed a meta-analysis on the efficacy of large doses of aspirin and found that it reduced the risk of colorectal cancer by 17% (RR- 0.83 95% CI, 0.72– 0.96). Several subsequent studies have confirmed this finding, with the exception being, studies that utilized smaller doses (A. T. Chan et al., 2006, 2008; Cook et al., 2005; Flossmann & Rothwell, 2007; Gann, Joann, Glynn, Buring, & Hennekens, 1993). In a study of Cox-2 selective inhibitors, Bertagnoli et al. (2006) showed that Celecoxib reduced the risk of colorectal adenoma by 33-45% (RR-0.67 95% CI 0.59–0.77 and RR- 0.55 95% CI 0.48–0.64, respectively) depending on the dose. It has also been shown that Celecoxib increases the risk of cardiovascular events, in those with an increased baseline risk for heart disease (Bertagnolli et al., 2009; Solomon et al., 2008). Unfortunately, many of the risk factors for heart disease and colorectal cancer are shared (On On Chan et al., 2007).

Summary

For all of the studied diseases, moderate to vigorous physical activity has been shown to be at least as effective, if not more effective than, pharmacological intervention. Furthermore, all pharmacological interventions discussed are recommended only for high risk populations due to adverse side effects.

The physical activity research is not without limitations, however. A majority of these meta-analyses were limited by the use of relative measures of physical activity (Low, Moderate, High). Furthermore, these analyses focused on aerobic training of moderate and vigorous levels, there was little mention of resistance training. Lastly, a majority of the analyses presented, used a single baseline measure of physical activity in the form of a survey or questionnaire. A single baseline measure may be problematic in that the follow up periods involved in these studies was generally on the order of 4-12 years and a single measure of physical activity over that period would not adequately describe possible changes. It is also well established that survey and questionnaire measures of physical activity grossly over represent objective measures of physical activity, as was discussed in the Estimates of Compliance section.

The American College of Sports Medicine Exercise is Medicine® Initiative

The American College of Sports Medicine has spearheaded the campaign to integrate physical activity into clinical practice with the Exercise is Medicine® initiative. The primary goal of this initiative is to encourage primary care physicians and other primary healthcare providers to promote physical activity within their patient populations. This health initiative promotes the practice of assessing and prescribing physical activity at the primary care level of the healthcare system, in an effort to reduce levels of population physical inactivity. It is unclear how effective this initiative, which started in 2007, has been, as there is little data available to quantify its progress or effect. Preliminary data are not promising as estimates of primary care practitioners that engage patients in physical activity assessment and prescription activities during office visits have remained stable at around the 30% mark from 1999 to 2010 (P. M. Barnes & Schoenborn, 2012; Wee, McCarthy, Davis, & Phillips, 1999).

The Exercise is Medicine® Healthcare Providers Action Guide (American College of Sports Medicine, 2016), provides a step by step guide towards the implementation of the Exercise is Medicine® process within an office visit, as well as resources for office use. The guide includes the following 5-step process, including suggested tools, for healthcare providers to follow and use, during all routine office visits, 1) assess patient physical activity levels, using the Physical Activity Vital Sign (PAVS) 2) assess patient physical activity ability, using the Physical Activity Readiness Questionnaire (PAR-Q) 3) counsel patients to increase physical activity, utilizing the Exercise Stages of Change model 4) prescribe physical activity to patients using handwritten prescriptions 5) provide patients with referrals to exercise professionals when deemed necessary.

Tools

The Physical Activity Vital Sign was developed at the University of Utah, Department of Family and Preventative Medicine, for use by clinicians (Golightly et al., 2017). The tool consists of two questions, 1) "On average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)?", and 2) "On average, how many minutes do you engage in exercise at this level?" (American College of Sports Medicine, 2016). In an effort to validate the Physical Activity Vital Sign Coleman et al. (2012) found that the results from a large-scale implementation of the Physical Activity Vital Sign into the electronic medical records of the Kaiser Permanente healthcare system were similar to the results of national surveys related to physical activity levels. This work showed that after a period of just one and a half years, it was possible to implement this tool into the electronic medical records of 86% of patients within the system. Further, Coleman et al. (2012) found a statistically significant, though clinically non-significant, relationship between the use of the Physical Activity Vital Sign and the outcome measures, weight loss and HBa1C, over time (Grant, Schmittdiel, Neugebauer, Uratsu, & Sternfeld, 2014).

The Physical Activity Readiness Questionnaire is a seven question screening tool used to determine whether or not patients have potential for negative heart and/or musculoskeletal related outcomes during engagement in physical activity (American College of Sports Medicine, 2016). A patient that answers “no”, to all seven questions is cleared for moderate intensity physical activity. A “yes” answer to any question is an indication that the patient is potentially at risk for a negative outcome from engagement in physical activity, and clinicians are advised to use their professional judgement in the prescription of physical activity in these cases.

The Exercise Stages of Change Questionnaire consists of five questions and is used to determine the “Stage of Change” that a patient is currently in (American College of Sports Medicine, 2016). The stages of change model stems from the transtheoretical model of behavior change, pioneered by James O. Prochaska and Carlo Di Clemente in the late 1970’s and early 1980’s (Glanz, Rimer, & Viswanath, 2008). The model, amended for use within the Exercise is Medicine® initiative, consists of five distinct stages of change ranging from precontemplation, the patient has no intention of becoming physically active, to maintenance, the patient has met the physical activity recommendations regularly for 6 consecutive months. This model was born from smoking cessation research and has been applied to multiple behavior change domains since. This is one of the many parallel approaches between the fight against smoking and the fight against physical inactivity.

Implementation and Efficacy

The Exercise is Medicine® initiative relies heavily upon primary care healthcare providers to implement the 5-steps into their daily clinical practice. However, providers are not financially incentivized to do so, and may not see the value in spending their time discussing physical activity with patients, especially when confronted with the myriad of other time-consuming tasks that they are responsible for executing (AuYoung et al., 2016; Huijg et al., 2015; Lobelo, Duperly, & Frank, 2008; Peterson, 2007; Vuori, Lavie, & Blair, 2013). Further, dissemination of these guides and their contents is not required within the medical school curriculum making it reasonable to assume that many healthcare providers may be unaware of the Exercise is Medicine® Initiative altogether (Sallis et al., 2016).

Little is known about the implementation or efficacy of the Exercise is Medicine® initiative as there is no data that directly reports outcomes related to either of these lines of query. What data is available does not support the notion that the initiative is being implemented in practice. In 1999, eight years prior to the inception of the Exercise is Medicine® initiative, Wee et al. (1999) reported that 34% of patients that had seen a doctor within the last twelve months reported receiving exercise related counseling. Thirteen years later (based on data from four years after the start of the initiative) Barnes and Schoenborn (2012) reported that 32.4% of patients reported the same result. This lack of change in exercise related counseling implies that the Exercise is Medicine® initiative is having little impact on the actions of primary care practitioners.

There have been no direct evaluations of the efficacy of the Exercise is Medicine® initiative. Indirect investigations into components of the 5-step process do not support the hypothesis that it is an effective strategy. AuYoung et al. (2016) states that "Findings on the impact of physical activity interventions in primary care have been mixed, due to insufficient follow-up or a lack of clarity about intervention intensity". Similarly, Eden, Orleans, Mulrow, Pender and Teutsch (2002) state that "Evidence is inconclusive that counseling adults in the primary care setting to increase physical activity is effective." These findings suggest that, although the Exercise is Medicine® initiative appears to have the support of major health institutions, including the American College of Sports Medicine, it may not be fully supported by the current literature. That is not to say that there are current reports that directly refute the current implementation status and efficacy of the project.

Summary

The Exercise is Medicine® initiative has been in operation for over a decade. In this time there have been no efforts to quantify whether or not it is being implemented into practice, or into the effect it is having on population physical activity levels. There is evidence that population physical activity levels are on the rise, however this trend cannot necessarily be attributed to the Exercise is Medicine® initiative, as it is unknown how many practitioners are aware of, and using, the 5-step process. There is clearly a gap in the literature for a critical analysis of the effectiveness of the EIM model in the clinical setting.

Chapter 3.

An Updated Assessment of The Clinical and Economic Burden of Physical Inactivity on the US Healthcare System and an Analysis for Potential Change

Abstract

Purpose

The present study builds on previous works that date back more than two decades and do not include critical diseases that have been shown to be modifiable through physical activity such as Alzheimer's disease, depression and breast cancer, by updating old analyses and including the most robust sample of diseases to date. Further, this is the first study to include an analysis of the potential ramifications of a national physical activity goal. The purpose of this analysis is to quantify the clinical and economic burden of physical inactivity on the US healthcare system, and to contextualize the effect of a realistic change in population physical activity levels according to the Healthy People 2020 goals, in an effort to help practitioners and policymakers alike, understand the impact of the promotion of physical activity on the US healthcare system for the following conditions: cardiovascular disease, type II diabetes, depression, Alzheimer's disease, breast cancer, colon cancer, and stroke.

Methods

Relative risks for each disease were retrieved from meta-analysis or systematic review, based on recency, quality, and number of included studies. Direct medical costs and prevalence estimates were retrieved from the most recent sources available. Population Attributable Risk (PAR) was calculated as PAR= (1+ P_{rf} x (RR-1))/(Prf x (RR-1)), where P_{rf} is the percentage of the U.S. population not meeting minimum exercise requirements and RR is the relative risk of disease for physically inactive, versus physically active

individuals. PAR was calculated for each disease under two conditions, based on differing previously-reported estimates of population physical inactivity levels; 56.6% and 90.4%. Main outcome measures include the annual number of clinical cases, and the total direct medical costs, attributable to physical inactivity for each disease, as well as potential savings in these terms, given successful completion of the Healthy People 2020 goals.

Results

Physical inactivity is responsible for between 19-28 million clinical cases and between USD 109-155 billion in direct medical costs, annually. Reducing population physical inactivity by 4.4 percentage points, the decline necessary to meet the Healthy People 2020 target, could potentially lead to a reduction of over 1 million cases and a savings of over USD 5 billion, annually. Moreover, a reduction in physically inactive persons by roughly 1 percentage point could potentially result in a quarter of a million cases of disease prevented and more than a billion dollars in savings, annually.

Conclusion

Healthcare practitioners and policymakers are in a position to effect population physical activity levels. Our results indicate that an increase in physical activity of less than 1% will lead to a quarter of a million cases prevented and over a billion dollars in savings. These findings alone should be enough to encourage the implementation of strategies aimed at increasing physical activity.

Introduction

Physical inactivity is a growing health concern within the United States. It is estimated that 56.5-90.4% of adult Americans do not meet the minimum weekly physical activity requirements of 150 minutes of moderate, or 75 minutes of vigorous, physical activity per week (Haskell et al., 2007). Recent evidence from the Prospective Urban Rural Epidemiology (PURE) study, suggests that failure to achieve these minimum weekly requirements is associated with a 20-35% greater risk of all-cause mortality (Lear et al., 2017). An established objective of the Healthy People 2020 campaign, a campaign updated decennially, directed at improving the health of all US citizens, is to increase the percentage of the U.S. population meeting the minimum weekly physical activity requirements by 10%, equivalent to a 4.4% decline in physically inactive persons.

There is currently an epidemic of diseases related to physical inactivity (Alzheimer's Association, 2015; Center for Behavioral Health Statistics and Quality, 2016; Mariotto et al., 2011; Mozaffarian et al., 2016b), with most studies indicating that the primary diseases related to a lack of adequate activity include cardiovascular disease, stroke, type II diabetes mellitus, Alzheimer's disease, depression, and breast and colon cancers. These diseases hold three factors in common: they are all top ten causes of death in the United States (depression via suicide) (National Center for Health Statistics, 2016), are all associated with high direct medical costs (DMC) (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Mariotto et al., 2011; Mozaffarian et al., 2016b; Wimo, Winblad, Jonsson, & Jo, 2010), and are all modifiable through physical activity intervention (Aune et al., 2015; Hamer & Chida, 2009; Johnson et al., 2013; Kyu et al., 2016; Sattelmair et al., 2011; Silveira et al., 2013; Wu et al., 2013).

The results of previous meta-analyses and systematic reviews on the interaction between physical activity and these diseases have shown that increasing physical activity is an effective preventative strategy, reducing the risk of developing any of these diseases by 12-45% (Aune et al., 2015; Hamer & Chida, 2009; Johnson et al., 2013; Kyu et al., 2016; Sattelmair et al., 2011; Silveira et al., 2013; Wu et al., 2013). Further, physical activity has been shown to be just as, if not more, effective than pharmacological intervention in treating these diseases (Alberti et al., 2007; Aune et al., 2015; Blondell et al., 2014; Cole et al., 2009; Diniz et al., 2009; Freedman et al., 2011; Hamer & Chida, 2009; Jeon et al., 2007; Johnson et al., 2013; Kyu et al., 2016; Law et al., 2009; Li et al., 2013; Li & Siegrist, 2012; Naci & Ioannidis, 2013; Robsahm et al., 2013; Sattelmair et al., 2011; Silveira et al., 2013; Francesco Sofi et al., 2008; Wegner et al., 2014; Wu et al., 2013). This efficacy-related evidence has spurred a push to implement physical activity as preventative medicine within the healthcare system. The American College of Sports Medicine has spearheaded the campaign to integrate physical activity into clinical practice with the Exercise is Medicine® initiative. This health initiative promotes the practice of assessing and prescribing physical activity at the primary care level of the healthcare system in an effort to reduce levels of population physical inactivity. It is unclear how effective this initiative, which started in 2007, has been, as there is little data available to quantify its progress. Preliminary data are not promising as estimates of primary care practitioners that engage patients in physical activity assessment and prescription activities, during office visits, have remained stable at around the 30% mark from 1999 to 2010 (P. M. Barnes & Schoenborn, 2012; Wee et al., 1999).

Although the burden of physical inactivity on the US healthcare system has previously been analyzed, it is important to update and build on our understanding, periodically. Previous analyses, using similar methods, date back more than two decades and do not include critical diseases that have been shown to be modifiable through physical activity such as Alzheimer's disease, depression and breast cancer. Also, these analyses failed to put the burden of physical inactivity into a context meaningful to current practitioners and policy makers.

Quantifying the burden of physical inactivity, in terms of number of clinical cases and direct medical costs in the United States, will help to contextualize the problem of physical inactivity, relative to other health concerns, for practicing clinicians. Then, analyzing the potential case- and cost-savings effect of a current physical activity initiative, will put into perspective how much change a program, such as the Healthy People 2020 campaign, can have on the US healthcare system. The objective of the study reported herein was to determine the number of clinical cases, the total direct medical costs attributable to physical inactivity and the potential case- and cost-savings effect, of a current physical activity initiative, for the following conditions: cardiovascular disease, type II diabetes, depression, Alzheimer's disease, breast cancer, colon cancer, and stroke.

Methods

Disease Inclusion Criteria

The diseases included in this study were selected based on three criteria. First, each disease had to be listed as a top ten cause of death in the United States according to the most recent statistics presented by the National Center for Health Statistics (National Center for Health Statistics, 2016). Second, the disease had to be associated with annual direct medical costs in excess of USD 15 billion. Lastly, the Relative Risk (RR) for each disease had to be shown to be modifiable through physical activity. A summary of disease type, disease prevalence, cause of death rank, direct medical cost, and the relative risks used for calculations, can be found in Table 1.

Prevalence

Estimates of disease prevalence were obtained following a systematic search of Pubmed, Google Scholar and SPORT discus. The most recent estimates available from the most reliable sources were selected.

Direct Medical Cost

Each direct medical cost estimate, which included cost of inpatient care, prescription medication, outpatient and office-based provider visits, hospitalization and hospital costs, physician cost, nursing home care and home health care, was obtained following a systematic search of Pubmed, Google Scholar and SPORT discus. The most recent estimate of direct medical cost was used in each case and adjusted, using the consumer price index, to 2016 USD.

Relative Risks

Meta-analyses and systematic reviews containing relative risk values for each disease were identified by searching PubMed, Google Scholar and SPORT discus. Articles were selected for use in this study based on recency, scope, and similarity of physical activity classification. For the purpose of this analysis, a participant was considered physically inactive if they failed to satisfy the weekly minimum exercise requirements of 150 minutes of moderate, or 75 minutes of vigorous activity, and physically active if they accomplished these requirements. Preference was given to studies that classified active and non-active individuals in these terms.

Population Attributable Risk

Population Attributable Risk (PAR) is an estimate of the proportion of the people within a diseased population attributable to a specific risk factor. In our case, the specific risk factor was physical inactivity. PAR was calculated for each disease, as it has been in similar studies (D. E. Barnes & Yaff, 2011; Katzmarzyk, Gledhill, & Shephard, 2000), using the formula:

$$PAR = (P_{rf} \times (RR-1))/(1 + P_{rf} \times (RR-1))$$

P_{rf} is the percentage of the U.S. population considered physically inactive and RR is the relative risk of disease for a physically inactive, compared to a physically active, individual.

Determination of P_{rf}

Citing NHIS survey data, the Healthy People 2020 goals campaign reports that, in 2008, 56.5% of US adults over the age of 18 were physically inactive. However, Tucker, Welk and Beyler (2011) analyzed 2005-2006 NHANES data and reported a large disparity in estimates of population physical inactivity based on study methodology. In their analyses, 38% of participants were considered physically inactive according to survey results, whereas 90.4% of adults were considered physically inactive when monitored for 7 consecutive days via direct accelerometry. For this reason, PAR was calculated twice. First PAR was calculated based on the NHIS survey data using a P_{rf} of 0.565, and second PAR was calculated based on NHANES accelerometry data using a P_{rf} of 0.904

Savings Analyses

The Healthy People 2020 goals campaign set a goal to increase the number of Americans satisfying the weekly minimum exercise requirements by 10%. This 10% increase in population physical activity represents a 4.4 percentage point decrease (56.5%-52.1%) in those considered physically inactive.

The first savings analysis (SurveyData) was conducted using the PAR estimate based on NHIS survey data and the assumption that a 10% increase in population physical activity was achieved, per the Healthy People 2020 goals campaign.

The second analysis (Accel10%) was conducted using the PAR estimate based on NHANES accelerometry data and the assumption that a 10% increase in population physical activity was achieved. Importantly, a 10% increase in the percentage of the population considered physically active, given that only 9.6% of the population was considered physically active at baseline, leads to an absolute decrease in those considered physically inactive, of only 0.96 percentage points; a much smaller absolute change than initially intended by the Healthy People 2020 goals campaign. For this reason, a third analysis was conducted.

The third analysis (Accel4.4) was conducted using the PAR estimate based on NHANES accelerometry data and the assumption that an absolute decrease in physical inactivity of 4.4 percentage points was achieved.

Potential Cases Prevented

Potential cases prevented for each analysis were calculated as:

Potential Cases Prevented= (PAR1 x Prevalence) - (PAR2 x Prevalence)

Where PAR1 was calculated using the baseline P_{rf}, and PAR2 was calculated using the P_{rf} given the accomplishment of the assumed goals. For the SurveyData analysis, PAR1 was calculated with the baseline P_{rf} of 0.565, and PAR2 was calculated using a P_{rf} of 0.521, representing a 10% increase in those considered physically active from baseline, and an absolute decrease in those considered physically inactive of 4.4 percentage points. For the Accel10% analysis, PAR1 was calculated with the baseline P_{rf} of 0.904, and PAR2 was calculated using a P_{rf} of 0.894, representing a 10% increase in those considered physically active from baseline. For the Accel4.4 analysis, PAR1 was calculated with the baseline P_{rf} of 0.904, and PAR2 was calculated using a P_{rf} of 0.860, representing an absolute decrease in those considered physically inactive of 4.4 percentage points from baseline.

Potential Savings in Direct Medical Costs

Potential savings in direct medical costs, for each condition and scenario were calculated as:

Potential DMC Savings = Potential Cases Prevented x DMC Per Case

Where DMC Per Case was calculated as:

DMC Per Case= Total Direct Medical Cost of Disease/Prevalence of Disease

Results

Total Clinical Cases and Direct Medical Costs Attributable to Physical Inactivity

When PAR was calculated for the SurveyData analysis, based on survey data from the NHIS, the total clinical cases attributable to physical inactivity for all diseases combined, annually, were 28.2 million. The total direct medical costs attributable to physical inactivity for all diseases combined were USD 154.61 billion, annually.

When PAR was calculated for both the Accel10% and Accel4.4 analyses, based on accelerometry data from the NHANES, the total clinical cases attributable to physical inactivity for all diseases combined, annually, were 19.5 million. The total direct medical costs attributable to physical inactivity for all diseases combined were USD 109.21 billion, annually.

Total clinical cases and direct medical costs attributable to physical inactivity for each disease are listed in Table 3.

SurveyData Analysis

The SurveyData analysis assumed that at baseline 56.5% of the population was physically inactive and that a 10% increase in population physical activity was achieved, reducing population physical inactivity by 4.4 absolute percentage points. This analysis estimated that 1,267,548 clinical cases would be prevented and USD 6.55 billion in direct medical costs would be saved, annually.

Accel10% Analysis

The Accel10% analysis assumed that at baseline, 90.4% of the population was physically inactive and that a 10% increase in population physical activity was achieved, reducing population physical inactivity by 0.96 absolute percentage points. This analysis estimated that 227,443 clinical cases would be prevented and USD 1.11 billion in direct medical costs would be saved, annually.

Accel4.4 Analysis

The Accel4.4 analysis assumed that at baseline, 90.4% of the population was physically inactive and that a reduction in population physical inactivity levels of 4.4 absolute percentage points was achieved. This analysis estimated that 1,051,640 clinical cases would be prevented and USD 5.17 billion in direct medical costs would be saved, annually.

All Analyses

For all analyses, cardiovascular disease was the disease type with the greatest number of Potential Cases Prevented, whereas type II diabetes mellitus was the disease type with the greatest Potential DMC Savings. Alzheimer's Disease was associated with the highest PAR values, whereas breast and colon cancer were associated with the lowest. These differences were due to their respective relative risk values. Alzheimer's Disease was associated with the highest DMC Per Case ($14,662.26) whereas cardiovascular disease was associated with the lowest ($2,192.52). A summary of the Potential Clinical Cases Prevented and Potential DMC Savings for each analysis are presented in Table 4.

Table 2 provides a summary of the relative risk for each disease studied, given both physical activity and pharmacological intervention. Although physical activity has been demonstrated to be as effective as pharmacotherapy in many settings, the adherence to physical activity is lower than pharmacologic intervention. It is important to note that all pharmacological interventions are associated with some level of negative side effects in a portion of the patient population. Whereas some level of physical activity can be prescribed to a large portion of the population as a preventative measure, with less regard for side effects. Physical activity has the advantage of working to treat all of the diseases related to physical inactivity at once as a "one size fits all" prescription.

Discussion

The primary findings of our analysis show that between 19-28 million cases of disease and between USD 109-154 billion in direct medical costs can be attributed to physical inactivity annually. Furthermore, our analysis is the first to demonstrate that a decrease in the percentage of the population considered physically inactive of 4.4 points (Healthy People 2020 goal), will lead to the prevention of more than 1 million clinical cases and over USD 5 billion in savings of direct medical costs annually, regardless of P_{rf} estimate. Impressively, a decrease in population physical inactivity levels of just 0.96 percentage points was shown to lead to a quarter of a million cases prevented and over USD 1 billion in direct medical cost savings, annually. These findings suggest that physical activity interventions capable of increasing the percentage of the population meeting the minimum weekly exercise requirements by as little as 1 percentage point may be worth USD 1 billion in direct medical cost savings. These results, combined with the knowledge that physical activity is as effective as pharmacological intervention, without the adverse side effects, gives considerable insight into the power of physical activity as a preventative medical intervention.

To date there have been two analyses of the economic burden of physical inactivity, using the population attributable risk method, on the US healthcare system (Colditz, 1999; Garrett, Brasure, Schmitz, Schultz, & Huber, 2004), and one global analysis that included the US, amongst 143 other countries (Ding et al., 2016). Colditz (1999) and Garrett, Brasure, Schmitz et al. (2004) relied upon data that is almost two decades old for their analyses, at a time when our understanding of the relative risk of disease, based on exercise status, was so limited that there was debate as to whether or not physical activity had a protective effect on breast cancer, and total healthcare spending was roughly one third of what it is today. Further, Garrett, et al. (2004) focused solely on the Minnesota healthcare system, providing no insight into the effects of physical inactivity nationwide. Ding, Lawson, Kolby-Alexander, et al. (2016) did not include Alzheimer's Disease or depression, the sixth and tenth (via suicide) leading causes of death in the US, respectively, in their analysis of the global burden of physical inactivity. Further, none of these reports quantify the number of cases of each disease attributable to physical inactivity or estimate the potential case and cost savings based on the proposed goals of a current national health initiative.

In an analysis of the economic costs of inactivity in the United States, Colditz (1999) found that physical inactivity, as defined by "no reported leisure time physical activity", cost between USD 38.27 and 58.58 billion (adjusted from 1995 to 2016 dollars), or between 2.4 and 3.7% of total healthcare spending, annually. Since that time, total healthcare spending has roughly tripled to 3.3 trillion dollars annually (Centers For Medicare and Medicaid Services, 2016). Based on our findings we can conclude that the cost of physical inactivity in the United States, USD 109-154 billion, has increased at a rate greater than inflation and the percentage of total healthcare spending due to physical inactivity, has potentially increased, as our data would suggest that it is currently between 3.3 and 4.7% (109B/3.3T, 1545B/3.3T).

Ding, et al. (2016), in a report on the global economic burden of physical inactivity, found the cost of physical inactivity in the US to be between 8.6 and 58.6 2013 international dollars, equivalent to between USD 8.86 and 60.37 billion in 2016. However, this analysis did not include Alzheimer's Disease or depression, which accounted for USD 47.0 and USD 64.8 billion dollars in our analysis, respectively. Removing the cost of these two diseases brings our estimate to between USD 62 and USD 89.2 billion.

In a study of the economic impact of physical activity on cardiovascular disease, Wang et al. (Wang, Pratt, Macera, Zheng, & Heath, 2004), found that 9.2 million cases and USD 23.7 billion in direct medical costs of cardiovascular disease were attributable to a lack of physical activity. These values fall within the ranges for total cases (NHIS Survey Data - 10,819,840, NHANES Accelerometry Data- 7,096,240) and DMC savings (NHIS Survey Data - $23.72 B, NHANES Accelerometry Data - $15.56 B) attributable to physical inactivity estimated for cardiovascular disease in our analyses.

Our analyses build on previous works by studying more disease states, calculating PAR under multiple conditions, and estimating the economic impact of changes to current levels of population physical inactivity according to real world goals.

Our findings also suggest that the economic burden of physical inactivity is similar to that of tobacco use. According to the American Cancer Society (Eriksen, Mackay, Schluger, Gomeshtapeh, & Drope, 2015), tobacco related healthcare costs have been estimated to be USD 133 billion annually and Xu et al. (2015) estimated that in 2010 smoking-attributable healthcare spending totaled USD 170 billion. Compare these estimates of tobacco related healthcare estimates to our findings of physical inactivity related healthcare costs of between USD 109-154 billion annually. In similar fashion, a year 2000 investigation into the economic burden of physical inactivity in Canada found that the healthcare costs attributable to physical inactivity and smoking were similar in the Canadian healthcare system (Katzmarzyk et al., 2000), as well. These findings suggest that efforts to reduce physical inactivity levels should be on par with those directed at reducing smoking levels.

Preferring lower but also more stringent and less speculative cost estimates, we considered direct medical costs only, and by not considering indirect and intangible costs associated with each disease, provide more defensible, though more conservative, estimates of economic burden. Furthermore, the results reported here are based on estimations of time spent participating in physical activity. No measure of fitness, or change in fitness due to physical activity, was accounted for, but should be incorporated in future studies. Conceivably, a research question to be evaluated concerns how the effects of improved physical fitness versus time spent participating in physical activity translate into healthcare savings. We also recognize the quality and relevance of our source data within the availability of quality estimates. Relative risk values were retrieved from the highest quality sources available; however, not all sources used the minimum weekly exercise recommendations as criterion for group stratification. Many such sources used relative values of physical activity, stratifying participants in to low and high activity groups. Direct medical cost and prevalence estimates were from the most recent sources available, however in a few cases these reports were from as far back as 2010. To stay on the conservative side, we adjusted all direct medical costs to 2016 dollars based on the general consumer price index (CPI), as the medical CPI is based on a narrower basket of goods and services and would have yielded even greater cost estimates. Here too, in keeping with our preference for lower and more robust estimates, we preferred a conservative approach. Lastly, in our estimate of P_{rf} for exposure to physical inactivity we had to reconcile several methods to determine the percentage of the population considered to be physically inactive. To resolve this, we calculated PAR under multiple conditions and scenarios.

Conclusion

Physical inactivity, an established problem in the US and several other Western countries, and of significant concern in evolving economies, has been linked convincingly to significant increases in clinical cases of multiple, highly prevalent diseases; in turn, with marked morbidity, mortality, and substantial direct medical costs. Physical inactivity has also been demonstrated to be just as, if not more, effective in treatment compared to pharmacological intervention, without the risk of adverse side effects.

Our analysis establishes that the clinical and economic burden of physical inactivity to the US healthcare system, both in terms of population affected and direct healthcare expenditures involved, parallels that of smoking. For this reason, public health initiatives aimed at reducing physical inactivity should be similar to those aimed at reducing tobacco use. Furthermore, our analysis demonstrated that a reduction in population physical inactivity levels of 4.4 percentage points, an established objective of the Healthy People 2020 campaign, will prevent over 1 million cases of disease, as well as savings of over USD 5 billion in direct medical costs, annually. Further, we found that a change in population physical activity levels of less than 1 percentage point could lead to a quarter of a million fewer cases of disease and over USD 1 billion in direct medical cost savings. These findings should encourage healthcare practitioners and policymakers alike to advocate for increased physical activity.

Chapter 4.

Assessment of Providers' Knowledge and Understanding of the American College of Sports Medicine Exercise is Medicine® Initiative

Abstract

Purpose

The Exercise is Medicine® (EIM®) initiative has proposed a strategy in which primary care practitioners advocate for increased physical activity within their patient populations, to increase population level physical activity. This strategy is heavily dependent upon the participation of primary care practitioners, however little is known as to the viewpoint of these practitioners related to this strategy. The purpose of this study is to assess primary healthcare providers familiarity with, current implementation of, and attitudes towards, the EIM® initiative.

Methods

A 5-section, random ordered, survey consisting of 30 questions, was distributed to 10,758 primary care practitioners in the united states, via email.

Results

Overall, primary care practitioners “neither agreed or disagreed” that it is within their scope of practice to be executing all five steps of the EIM® process at every office visit. Whereas, they “somewhat agreed” that four out of the five steps of the EIM® process are within their scope of practice. Of the primary care practitioners surveyed, 68.27% had never heard of EIM® initiative, and only 5.77% of respondents had heard of the initiative, knew of its purpose and were aware of the 5-step process. On a scale ranging from strongly agree, to strongly disagree, primary care practitioners “did not agree or

disagree" that the strategy proposed by the EIM® is within their scope of practice. It was also found that doctors are less likely than non-doctors to support the EIM® process. Zero respondents indicated that they thought the 5-step EIM® process would have a negative effect on population physical activity, while 73.08% of respondents felt that it would slightly increase population physical activity levels.

Conclusion

Our findings suggest that a large proportion of primary care practitioners are unaware of the EIM® initiative and they do not feel that the proposed strategy is within their scope of practice. However, they do feel that it would have only a positive impact on population physical activity levels. Importantly, doctors are less likely than non-doctors to agree that they should be executing all of the steps of the 5-step process at every office visit. Our findings suggest that primary care practitioners are largely unaware of the Exercise is Medicine® initiative and they do not feel that it is within their scope of practice. Based on these findings, it is recommended that the EIM® initiative increase visibility of their program, educate primary care practitioners as to how to implement the program, and take steps towards reducing the amount of time required of practitioners. These steps should include a streamlined version of the 5-step process, as well as transitioning the 5-step process to annual use.

Introduction

The American College of Sports Medicine (ACSM), among other health and exercise institutions around the world, recommends 150 minutes of moderate, or 75 minutes of vigorous intensity physical activity per week in order to promote and maintain good health(Haskell et al., 2007). Recent evidence from the Prospective Urban Rural Epidemiology (PURE) study supports these standards, as failure to achieve them is associated with a 20-35% increased risk for all-cause mortality (Lear et al., 2017). In an effort to increase the proportion of the population accomplishing the recommended levels of physical activity, the ACSM established the Exercise is Medicine® (EIM) initiative in 2007.

Multiple efforts have been made to quantify the proportion of the U.S. population that regularly meet the weekly recommendations for physical activity. Differences in methodological approaches has led to a wide range of estimates making interpretations difficult (Troiano et al., 2008; Tucker et al., 2011). For example, Tucker et al. (2011) found a discrepancy between self-reported data and data collected via 7-day continuous accelerometry. In this report, 62.0% of Americans met the weekly physical activity requirements when asked to self-report, whereas only 9.6% of Americans met the requirements according to accelerometry data. In an earlier report, Troiano et al. (2008) found similar discrepancies between self-report and accelerometry methods, and suggested that great care must be taken when interpreting self-reported physical activity data. However, the authors also suggested that the two methods are similarly discrepant regarding patterns of activity across gender and age groups. More recent reports, based on self-reported data, suggest a pattern of increased physical activity amongst U.S. adults between 2008-2015. Specifically, the proportion of U.S. adults meeting weekly physical activity requirements has increased from 43.5% in 2008, to 49.8% in 2015, with a peak of 50% in 2012 (US Department of Health and Human Services, 2014).

Increasing the proportion of the population that meets the weekly physical activity requirements is an important goal, as meeting these requirements is associated with up to a 45% reduced risk of lifestyle diseases (Aune et al., 2015; Hamer & Chida, 2009; Johnson et al., 2013; Kyu et al., 2016; Sattelmair et al., 2011; Silveira et al., 2013; Wu et al., 2013) including cardiovascular disease, stroke, type II diabetes mellitus, Alzheimer's disease, breast cancer, colon cancer and depression (Rourk, Abraham, Olson, & Snyder, 2018). Further, physical activity intervention has been shown to treat these diseases as well as, or better than, pharmacological intervention (Cole et al., 2009; Diniz et al., 2009; Freedman et al., 2011; Law et al., 2009; Naci & Ioannidis, 2013).

These particular lifestyle diseases, taken as a group, have reached epidemic levels with an estimated combined prevalence of over 145 million diagnosed cases and direct medical costs in excess of USD 605 billion, annually (Rourk, Abraham, et al., 2018). Further, between 19 and 28 million of these diagnosed cases and between USD 109 and 154 billion of the associated direct medical costs have been attributed to physical inactivity (Rourk, Abraham, et al., 2018). It has been estimated that an increase in the proportion of the U.S. population that meets the weekly physical activity requirements by 4.4 absolute percentage points can lead to the prevention of over 1 million diagnosed cases and a savings in excess of USD 5 billion in direct medical costs, annually (Rourk, Abraham, et al., 2018).

The prevalence and costs associated with physical inactivity, combined with the preventative efficacy of physical activity, led to the establishment of the Exercise is Medicine® initiative by the American College of Sports Medicine (ACSM) in 2007. The primary goal of this initiative is to encourage primary care physicians and other healthcare providers to promote physical activity within their patient populations (American College of Sports Medicine, 2016). The Exercise is Medicine®, Healthcare Providers Action Guide (American College of Sports Medicine, 2016), provides a step by step guide towards the implementation of the Exercise is Medicine® process within an office visit, as well as resources for office use. The guide includes the following 5-step process for healthcare providers to follow during all routine office visits, 1) assess patient physical activity levels, using the Physical Activity Vital Sign (PAVS), 2) assess patient physical activity ability, using the Physical Activity Readiness Questionnaire (PAR-Q), 3) counsel patients to increase physical activity, utilizing the Exercise Stages of Change model, 4) prescribe physical activity to patients using handwritten prescriptions, and 5) provide patients with referrals to exercise professionals when deemed necessary.

The Exercise is Medicine® initiative relies heavily upon primary care healthcare providers to implement these steps into their daily clinical practice. However, providers are not financially incentivized to do so, beyond their normal care, and may not recognize the value in spending clinical time discussing physical activity with patients, especially when confronted with the myriad of other time-consuming tasks that they are responsible for (AuYoung et al., 2016; Huijg et al., 2015; Lobelo et al., 2008; Peterson, 2007; Vuori et al., 2013). Further, dissemination of these guides and their contents is not required within the medical school curriculum, making it reasonable to assume that many healthcare providers may be unaware of the Exercise is Medicine® Initiative altogether (Sallis et al., 2016).

While previous studies have assessed barriers to the implementation of physical activity based healthcare strategies by healthcare professionals (AuYoung et al., 2016; Huijg et al., 2015; Vuori et al., 2013), no study has focused on the attitudes of the primary care practitioner towards the Exercise is Medicine® initiative. Due to the reliance on the primary care practitioner to execute the Exercise is Medicine® initiative, it is vitally important to understand their perspective. The purpose of this study is to assess primary healthcare providers familiarity with, current implementation of, and attitudes towards, the Exercise is Medicine® initiative.

Methods

Study Population

A random sample of 10,003 healthcare providers nationwide, including 1,429 of each, family practitioners, pediatricians, geriatricians, internists, obstetrician-gynecologists, nurse practitioners and physicians assistants was generated from the American Medical Association (AMA) Masterfile database by way of the third-party licensor, Redi-Data. A convenience sample of 755 family practitioners, internal medicine/pediatric physicians and pediatricians, practicing in North Dakota, South Dakota, Minnesota, Wisconsin and Iowa was procured from the marketing department of a local hospital.

For inclusion, practitioners had to be currently practicing, with primary care patients as a part of their patient population.

Survey Instrument

With the assistance of experts in survey design from the Office of Measurement Services at the University of Minnesota, the survey instrument used in this study was designed to assess the primary healthcare providers familiarity with, current implementation of, and attitudes towards, the Exercise is Medicine® initiative. A copy of the full survey can be found in the appendix. In all cases, the first and second sections of the survey were presented in order. In the first section demographic information was obtained and included: specialty type, medical training type (Medical Doctor or Doctor of Osteopathy), the percentage of primary care patients seen in practice, career length, practice type, sex, date of birth and state in which practice is conducted. The second section included a description of the Exercise is Medicine® initiative, along with a description of the 5-step Exercise is Medicine® process outlined in the action guide and a single question directed at their familiarity with the initiative and the process. After the first two sections were answered, sections three through five were presented in random order, to control for any potential order effects. Section three contained questions related to the participants current clinical use of any, and/or, all of the steps of the Exercise is Medicine® 5-step process. The fourth section contained questions related to whether or not participants felt that any, and/or, all of the steps of the Exercise is Medicine® process are within their scope of practice. The fifth section of the survey contained the single question, “If all 5 steps of the EIM® process were carried out by all primary care practitioners during all office visits, how would the physical activity level of the patient population be affected?”. This question was intended to assess participants attitudes towards the potential efficacy of the Exercise is Medicine® initiative.

The survey was pretested by a focus group of four primary care practitioners for ease of use, timing and completeness.

The Cronbach’s Alpha test was used to verify reliability of the survey. Each respondent’s average response to the five questions in section four directed at understanding practitioners attitude towards each individual step of the EIM® process falling within their scope of practice, was compared to their response to a question in which respondents were asked if executing all five steps of the EIM® process was within their scope of practice. This analysis revealed a Cronbach’s Alpha of .871, demonstrating that the survey is indeed, reliable.

Statistical Methods

Prior to collecting data, a sample size calculation assuming a power of 0.80, an alpha of 0.05 and a moderate effect size of 0.3 resulted in a minimum sample requirement of 88 completed surveys.

Overall data was presented as percentage of total respondents.

For post-hoc comparison analyses between awareness status (Aware vs. Unaware), geographical status (MN vs. Non-MN) and medical degree status (Doctor vs. Non-Doctor), answers to questions were scaled one through seven, where 1 represented strongly agree and 7 represented strongly disagree, to allow for comparison of means in accordance with recent statistical recommendations from the literature (de Winter & Dodou, 2010; Wadgave & Khairnar, 2016). Means were compared by way of Levene's test for equality of variances and two-tailed t-tests.

To determine the effect of geographical status, medical degree status or an interaction between the two, a 2 x 6 ANOVA was performed on the questions from section 4 that were found to have significant between group differences under both analyzed conditions. An alpha level was set at 0.05 for determination of statistical significance. All statistical analyses were performed using SPSS (IBM, Armonk, New York).

Results

Out of a sample of 10,758, we received 104 completed surveys. Overall, 82% of respondents were doctors, of which 87% described themselves as medical doctors. Family practitioners represented 46% of the overall respondents and 56% of the doctors, whereas nurse practitioners represented 13% of the overall respondents and 74% of the non-doctors. Overall, 79% of respondents reported that between 76 and 100% of their patients seen in practice were primary care and 62% of respondents reported being in practice for greater than 15 years. The average age was 52.27 with a range between 32 and 78. Full results can be found in Table 5.

In section four, respondents were asked about their attitude towards the EIM® initiative and their scope of practice. These questions were scored on a 7-point likert scale, ranging from “strongly agree” (1) to “strongly disagree” (7), with the option to “neither agree nor disagree” (4). Results from section four indicated that overall, primary care practitioners “neither agreed or disagreed” that they should be executing all five steps of the EIM® process at every office visit. Respondents “somewhat agreed” that four out of the five steps of the EIM® process are within their scope of practice (range- 2.57-3.26). On average, respondents “neither agreed or disagreed”, that handwriting prescriptions was within their scope of practice as the average response was 3.95. Full results, questions and possible responses can be found in Figures 1 and 2.

Results from section two of the survey indicated that 68.27% of the primary care practitioners surveyed had never heard of Exercise is Medicine®. Only 5.77% of respondents had heard of the initiative, knew of its purpose and were aware of the 5-step process. A post-hoc analysis comparing the 5.77% of practitioners that were aware of the EIM® to those that were not revealed that the two groups do not execute the steps of the EIM at differing levels, with the exception being that primary care practitioners aware of the EIM® are more likely to use the Exercise Stages of Change model when implementing behavioral counseling strategies with their patients. Complete results from this section can be found in Figure 3.

Results from section three indicated that 91.35% of surveyed primary care practitioners self-reported that they never use all five steps of the EIM® process with their patients. Further, 98.02%, 96.55% and 60.92% of respondents indicated that they did not use the

PAVS, the PAR-Q and the Exercise Stages of Change model, respectively, when carrying out the associated step in the process. Full results from section three can be found in Figures 4-7.

In section five, zero respondents indicated that they thought the 5-step EIM® process would have a negative effect on population physical activity, while 73.08% of respondents felt that it would slightly increase population physical activity levels. Complete results are shown in Figure 8.

Of the completed surveys, 39 (37.5% of all respondents) came from the random sample of 10,003 healthcare providers, whereas 65 (62.5% of all respondents) came from the convenience sample of 755 midwestern physicians. Of the 65 surveys from the convenience sample, 59 (56.7% of all respondents) were completed by primary care practitioners practicing in the state of Minnesota. This discrepancy in response rate, related to geographical location, is likely attributable to the fact that the email contained University of Minnesota logos, per university research guidelines. In total, 24 states were represented, however the average number of representative surveys per state was 1.9, excluding surveys from Minnesota based respondents.

Due to this sampling issue, survey results were compared between Minnesotan and non-Minnesotan respondents. It was discovered that the Minnesotan respondents were significantly more likely to be doctors as compared to non-doctors. This led to a secondary comparison of medical degree status (doctor vs. non-doctor). In both secondary analyses, significant differences in response were found in section four, for questions 48-51 and 53. The results of these analyses are summarized in Figures 9 and

10. To determine the effect of medical degree status, geographical status, or an interaction, a 2 x 6 ANOVA was performed. According to the ANOVA analysis, the effect of medical degree status was significant for four questions in which respondents were asked how strongly they agreed with statements that asked if they should be, “assessing patient physical activity levels”, “utilizing behavioral counseling strategies directed at increasing physical activity”, “providing written prescriptions for physical activity”, or “executing all 5 steps of the EIM® process”, during every office visit. Geographical status was not significant for any question, and there was no interaction.

Discussion

The purpose of this study was to assess, via survey, primary healthcare providers familiarity with, current implementation of, and attitudes towards, the Exercise is Medicine® initiative. Our results suggest that primary care providers, regardless of medical degree status or geographical location, are largely, unaware of the Exercise is Medicine® initiative. Given the limited awareness of the Exercise is Medicine® initiative it is not surprising that 91.35% of respondents admit to never executing all 5 steps of the Exercise is Medicine® process with their patients. When analyzed separately, doctors “somewhat disagreed”, when asked if executing all five steps of the Exercise is Medicine® process at every office visit is within their scope of practice. Less beleaguering are the findings that none of the primary care providers surveyed, thought that the Exercise is Medicine® process would have a negative impact on patient physical activity levels. When asked how the implementation of the Exercise is Medicine®

initiative would affect the population physical activity level, the majority of providers stated that they believed it would slightly increase physical activity levels.

In a survey of patients published in 1999 using data from 1995, 12 years before the initiation of the Exercise is Medicine® Initiative, Wee, McCarthy, Davis and Phillips (Wee et al., 1999), found that 34% of respondents that had seen a doctor in the past 12 months were counseled to engage in physical activity. Similarly, in 2012 the NCHS reported that 32.4% of patients surveyed in 2010, three years after the creation of the Exercise is Medicine® initiative, that had seen a doctor in the past 12 months were counseled to engage in physical activity(P. M. Barnes & Schoenborn, 2012). Based on these findings it may seem logical to conclude that roughly one-third of doctors engage patients in physical activity related healthcare strategies, however, our findings suggest that doctors use discretion when choosing which patients to implement exercise related healthcare strategies and that they don't necessarily follow the Exercise is Medicine® strategy. This trend is especially true in the case of the first three steps of the process (physical activity level assessment, physical activity ability assessment and behavior change counseling), where at least 83.65% of respondents claimed to execute each of the steps with at least 1% of their patients for each step. The last two steps of the Exercise is Medicine® process (providing a handwritten prescription and referral to an exercise professional) are far less likely to be executed during a patient visit however, with 62.5% and 45.2% of respondents claiming to have never executed these steps, respectively, with their patients.

Though it has been demonstrated that the Physical Activity Vital Sign can be implemented within a large healthcare system (Coleman et al., 2012), the results of our study suggest that its use has not been widely adopted. The same can be said of all of the tools suggested to be used within the Exercise is Medicine® process, as, of the practitioners that do implement the steps associated with the Physical Activity Vital Sign, Physical Activity Readiness Questionnaire and Exercise Stages of Change model, 98.02%, 96.55% and 60.92%, of them, respectively, do not use the corresponding tool. When asked, what tools practitioners are using to accomplish these steps, an overwhelming majority of write in responses listed a variation of informal conversation without documentation. The lack of use of these tools, may be related to the lack of awareness of their existence.

The responses from section three suggest that doctors and non-doctor primary care practitioners are currently executing the steps of the Exercise is Medicine® initiative at the same rate. In section four, respondents were asked if they felt that it was within their scope of practice to execute each individual step of the 5-step process during office visits. In the final question of the section, respondents were asked if they felt it was within their scope of practice to execute all 5 steps of the 5-step process during all office visits. Significant differences were found between doctors and non-doctors for each question, where doctors were less likely to agree that each step, or all steps, were within the scope of their practice. The exception was question 52, in which respondents were asked if it was within their scope of practice to refer patients to exercise professionals, when they deem it appropriate. Though the average response to this question was not statistically different, doctors “somewhat agreed” (2.59) whereas non-doctors “agreed” (2.47). Though doctors agreed less than non-doctors for each question in section four, both groups did agree that it is within their scope of practice to assess patient physical activity level, assess patient physical ability level and refer to exercise professionals. However, doctors “neither agree or disagree” that the steps of behavioral counseling and handwriting prescriptions, are within their scope of practice. Further, doctors “somewhat disagree” that executing all five steps of the 5-step process is within their scope of practice. These findings suggest that doctors do not necessarily believe that the 5-step process proposed by the Exercise is Medicine® initiative is within their scope of practice. These finding are of great concern, as under its current construction, the implementation of the Exercise is Medicine® 5-step process is dependent on primary care physicians.

It should be noted that we received four emails objecting to the wording of the questions in the fourth section of the survey, all from medical doctors. The questions in this section purposefully included the phrase “during all office visits” as that is the mandate of the Exercise is Medicine® initiative; except in the case of the fifth step (referral to exercise professionals), as this step is recommended to be executed only when deemed necessary. All four of the emails we received stated that this wording forced them to change their answers from some form of agreement to some form of disagreement. Further, three of the four emails also included a suggested compromise, in which practitioners be asked to perform the 5-step process annually as opposed to at every visit. Below, a quote from one of the respondents:

“The survey may not reflect providers’ view of the importance of exercise. The use of ‘all clinic visits’ is not appropriate or practical. No provider will, or should, assess exercise at all, or even most, visits. You may want to change the wording to something like “all routine annual exams or annual check-ups”. Even then, 5-10 minutes to discuss only exercise is a big ask, even if important. Remember that these visits may only be scheduled for 20-30 minutes and includes time for rooming. Exercise is only part of a larger picture of health.”

While four emails are a small percentage (3.8%) of the total responses (104), it is reasonable to assume that other respondents had similar feelings, but did not take the time to reach out. These unexpected responses indicate that a move, on the part of the Exercise is Medicine® initiative, to an annual strategy may improve practitioner attitudes towards, and thus compliance with, the initiative.

The results of this survey are limited by a lack of random sampling for the midwestern group of practitioners. Though what originally appeared to be a geographical bias, was found to be a difference related to medical degree status. Another limitation was the failure to foresee and control for the objection to the wording of the questions in section four. Though the wording of the questions was purposeful, follow up questions aimed at delineating a respondents’ specific rationale for agreement or disagreement would have been illuminating. Lastly, this survey was limited by a low response rate. Though the response rate was in the range that can be expected for a single email distribution, more funding would have allowed for follow up emails, and likely would have improved the response rate.

Conclusion

To our knowledge this is the first survey of primary care practitioners with the aim of assessing their familiarity with, current implementation of, and attitudes towards, the Exercise is Medicine® initiative. Our findings suggest that primary care practitioners are largely unaware of the Exercise is Medicine® initiative and they do not feel that it is within their scope of practice. However, they do feel that it would have only a positive impact on population physical activity levels. Importantly, doctors are less likely than non-doctors to agree that they should be executing all of the steps of the 5-step process at every office visit. Based on these findings additional efforts to publicize the Exercise is Medicine® initiative is imperative. A campaign directed at educating primary care practitioners appears necessary, as so few practitioners are aware of the initiative. Further, steps towards reducing the amount of time required of primary care practitioners should be made, as this is a chief complaint. These steps should include a streamlined version of the 5-step process as well as transitioning the 5-step process to annual use, aligning with the attitudes of primary care physicians. The disconnect between primary care practitioner attitudes and the current construction of the EIM® strategy warrants an investigation of the 5-step process, along with recommended updates.

Chapter 5.

A Critical Evaluation of the Exercise is Medicine® Initiative and Proposed Amendments

Abstract

Purpose

The purpose of this editorial is to critically review the current Exercise is Medicine® (EIM) strategy to increase population physical activity through primary care practitioner intervention. The EIM® was established in 2007 by the American College of Sports Medicine (ACSM) and little has been done in an effort to assess the efficacy of the 5-step strategy that is currently in place.

Critical Evaluation

A critical review of the EIM® initiative and its 5-step process finds a dearth of direct and substantive evidence in support of its current construction. Individually, the steps of the 5-step EIM® process, and the tools associated with them, have not been shown to be implemented in practice or effective. The little evidence available to quantify primary care practitioners' awareness and use of the process, in the practical clinical setting, suggests that it has not been well implemented and is not well received.

Proposed Amendments

The Physical Activity Vital Sign (PAVS) and Physical Activity Readiness Questionnaire (PAR-Q) should be required within the electronic medical record systems of all hospitals and clinics nationally. Primary care practitioners should be responsible for assessing patient activity levels and ability through these tools at every office visit. They should then refer patients to exercise professionals at their discretion. To facilitate this referral

process it should be the responsibility of EIM® planners to develop an effective and easy to use referral network of exercise professionals. Further, it is the responsibility of the EIM® to increase visibility of this amended strategy, as well as to create surveillance system with the purpose of monitoring the efficacy and implementation of said strategy.

Conclusion

The current version of the EIM® strategy relies too heavily upon the primary care practitioner. Of chief concern are the lack of perceived time available and the lack of support for the current strategy, by the primary care practitioner. The proposed amendments provided herein are directed at better positioning both the primary care practitioner and the EIM® in order to more effectively utilize resources, lending to increased implementation and efficacy.

Introduction

The physiological benefits of exercise, particularly aerobic exercise, related to disease prevention and treatment, are clear. Further, economic analysis of the potential impact of exercise on the healthcare system support the use of exercise prescription in the clinical setting (Rourk, Abraham, et al., 2018). Despite this understanding, the implementation of exercise as a preventative and treatment intervention in the healthcare system is largely at a standstill. The Exercise is Medicine® (EIM®) Initiative, established in 2007 by the American College of Sports Medicine (ACSM), was developed to take on the challenge of bridging the gap between our understanding of the potential impact of exercise as medicine and its use in practice. After more than a decade as the champion of this movement, the EIM® initiative is due for a critical evaluation.

The EIM® initiative has remained unchallenged since its inception. There have been many editorials in which "calls to action" have been made in support of the initiative with little in the way of push back, potentially due to a lack of meaningful research on the topic. From a review of scholarly material related to the EIM® initiative, it appears that most researchers and medical professionals are theoretically supportive. However, despite this support, there is little evidence that the proposed strategy has been implemented in practice, much less effective.

The strategy outlined by the EIM® Healthcare Providers' Action Guide (American College of Sports Medicine, 2016), an ACSM publication, consists of five steps to be carried out by the primary care practitioner. Also, the action guide encourages primary care practitioners to generally promote physical activity in the clinic setting by, "walking the walk", i.e. self-involvement in physical activity and leading by example. According to the Action Guide, the 5-step process for healthcare providers to follow during all routine office visits is as follows, 1) assess patient physical activity levels, using the Physical Activity Vital Sign (PAVS), 2) assess patient physical activity ability, using the Physical Activity Readiness Questionnaire (PAR-Q), 3) counsel patients to increase physical activity, utilizing the Exercise Stages of Change model, 4) prescribe physical activity to patients using handwritten prescriptions, and 5) provide patients with referrals to exercise professionals when deemed necessary.

Critical Evaluation

Step 1: Assess Patient Physical Activity Levels Using the PAVS Tool

The PAVS tool consists of two questions, 1) "On average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)?", and 2) "On average, how many minutes do you engage in exercise at this level?" (American College of Sports Medicine, 2016). In an effort to validate the Physical Activity Vital Sign Coleman et al. (2012) found that the results from a large-scale implementation of the Physical Activity Vital Sign, into the electronic medical records system of the Kaiser Permanente healthcare system, were similar to the results of national surveys related to physical activity levels. This work showed that after a period of just one and a half years, it was possible to implement this tool into the electronic medical records system of 86% of patients within the system. Further, works have found a statistically significant, though clinically non-significant, relationship between the use of the PAVS tool and the outcome measures, weight loss and HBa1C, over time (Grant et al., 2014).

Though the PAVS tool was validated for use in the healthcare system, and found to be associated with statistically significant changes in weight loss and HBa1C measures, the differences were not clinically significant (Grant et al., 2014). Statistical significance of non-clinically significant changes in weight loss and HBa1C measures was likely a result of large power due to a large sample size, as over 1.5 million visits by 696,267 adults to 1,196 primary care providers were studied.

The use of the PAVS tool was within the Kaiser Permanente healthcare system, appears to be unique, as a recent national survey found that 97.12% of primary care practitioners assess patient physical activity levels in greater than 1% of their patient populations (Rourk, Olson, & Snyder, 2018). However, of those that do assess activity levels, 98.02% do not use the PAVS tool. The most common approach to physical activity level assessment was informal conversation without record keeping.

Step 2: Assess Patient Physical Activity Ability Using the PAR-Q Tool

The PAR-Q is a seven question screening tool used to determine whether or not patients have potential for negative heart related and/or musculoskeletal outcomes during engagement in physical activity (American College of Sports Medicine, 2016). A patient that answers “no”, to all seven questions is cleared for moderate intensity physical activity. A “yes” answer to any question is an indication that the patient is potentially at risk for a negative outcome from engagement in physical activity and clinicians are advised to use their professional judgement in the prescription of physical activity in these cases.

According to survey, 83.65% of primary care practitioners assess physical activity ability level in at least 1% of their patient populations. However, similar to the PAVS tool, 96.55% of those practitioners that do assess physical activity level do not use the PAR-Q, again informal conversation without documentation was the most common reported method.

Similar to the PAVS tool, the PAR-Q is not meant to, and has not been demonstrated to, affect physical activity behavior of patients, rather these tools are designed to assess physical activity levels and ability, respectively.

Step 3: Utilize Behavior Change Counseling Strategies Including the Exercise Stages of Change Questionnaire

The Exercise Stages of Change Questionnaire consists of five questions and is used to determine the “Stage of Change” that a patient is currently in (American College of Sports Medicine, 2016). The stages of change model stems from the transtheoretical model of behavior change pioneered by James O. Prochaska and Carlo Di Clemente in the late 1970’s and early 1980’s (Glanz et al., 2008). The model, amended for use within the EIM® initiative, consists of five distinct stages of change ranging from precontemplation, the patient has no intention of becoming physically active, to maintenance, the patient has met the physical activity recommendations regularly for six consecutive months. This model was born from smoking cessation research and has been applied to multiple behavior change domains since. This is one of the many parallel approaches taken, between the fight against smoking and the fight against physical inactivity.

As it applies to physical activity, there is not a clear positive relationship between behavior counseling strategies and actual behavior change. AuYoung et al. (2016) states that “Findings on the impact of physical activity interventions in primary care have been mixed, due to insufficient follow-up or a lack of clarity about intervention intensity”. Similarly, Eden, Orleans, Mulrow, Pender and Teutsch (2002) state that “Evidence is inconclusive that counseling adults in the primary care setting to increase physical activity is effective.” It is worth noting that the “intensity” of behavior change counseling strategies found in the literature, and commented on by AuYoung et al. (2016) and Eden et al. (2002) is far greater than the proposed 3-5 minute session in which counseling is one of five steps.

In its current form, the 5-step process of the EIM® initiative, relies heavily upon the Exercise Stages of Change behavior change counseling strategy to affect patient physical activity behavior. However, there is not enough evidence to conclude that this type of counseling strategy is effective. Further, of the 83.65% of primary care practitioners that self-reported to use behavioral counseling strategies directed at increasing physical activity with at least 1% of their patient populations, only 39.08% use the Exercise Stages of Change Model. Motivational interviewing techniques and informal conversation were the two most common methods reported.

Step 4: Provide Handwritten Exercise Prescriptions to Patients

The EIM® process asks primary care practitioners to give handwritten prescriptions for exercise to patients. This directive is based on the findings from a randomized controlled trial with a six week follow up, in which handwritten prescriptions were found to be superior to simple verbal advice in affecting physical activity levels (Swinburn, Walter, Arroll, Tilyard, & Russel, 1998). Not considered in this trial are the motivations and attitudes of the primary care practitioners tasked with this directive. In a survey, primary care practitioners, on average, “did not agree or disagree” with a statement that read “Primary care practitioners should be providing written prescriptions for physical activity during all office visits, it is within their scope of practice.” (Rourk, Olson, et al., 2018). In the same survey, 62.50% of respondents self-reported that they never provide patients with handwritten prescriptions for physical activity. This evidence demonstrates that primary care practitioners are not eager to provide handwritten prescriptions for physical activity.

Similar to step three, step four, of the 5-step process of the EIM® initiative, is directed at changing patient physical activity behavior. Though there is evidence to support its efficacy, there is also evidence that suggests it will be difficult to implement in the primary care setting, primarily due to resistance from primary care practitioners.

Step 5: Provide Patients with Referrals to Exercise Professionals

Though it seems logical to refer patients in need of exercise to exercise professionals, this is a step that seems to be outside of clinical norms. The EIM® action guide holds primary care practitioners responsible for cultivating their own network of exercise professionals. Three pages of the guide are dedicated to the steps required to develop this network. Interestingly, when surveyed, primary care practitioners agreed with the statement "Primary care practitioners should be referring patients to exercise professionals when they deem it necessary, it is within their scope of practice.", however, 45% of the same practitioners admitted to never referring a patient to an exercise professional and a combined 91% referred less than 20% of their patients to exercise professionals.

As lack of time and other resources is a primary perceived barrier to the implementation of physical activity intervention by primary care practitioners (Huijg et al., 2015), adding the task of developing a network of exercise professionals will likely dissuade many practitioners from executing this step of the EIM® process.

Summary

Individually, the steps of the 5-step EIM® process, and the tools associated with them, have not been shown to be implemented in practice or effective. Overall, little is known about the implementation and efficacy of the EIM® initiative as there is little data that directly reports outcomes related to these areas of interest. What data is available, does not support the notion that the initiative is being executed in practice. In 1999, eight years prior to the inception of the EIM® initiative, Wee et al. (1999) reported that 34% of patients that had seen a doctor within the last twelve months reported receiving exercise related counseling. Thirteen years later (data from four years after the start of the initiative) Barnes and Schoenborn (2012) reported that 32.4% of patients reported the same result. This lack of change in exercise related counseling implies that the EIM® initiative is having little impact on the actions of primary care practitioners, who are integral to its implementation.

In a survey of primary care practitioners it was shown that only 5.77% of respondents were aware of the EIM® initiative, its purpose and the 5-step process and a startling 68.27% of respondents had never heard of the initiative (Rourk, Olson, et al., 2018). Further, primary care practitioners responded neutrally when asked if they felt that the 5-step EIM® process was within their scope of practice. When analyzed separately, physicians “slightly disagreed” with the same question.

A critical review of the EIM® initiative and its 5-step process finds a dearth of direct and substantive evidence in support of its current construction. The little evidence available to quantify primary care practitioners’ awareness and use of the process, in the practical clinical setting, suggests that it has not been well implemented and is not well received. Based on these findings, it is not clear how this model has garnered such unimpeded support in the academic realm.

Proposed Amendments

A critical evaluation of the current EIM® model necessitates amendments to the model. This section details these amendments while providing evidence for their proposal. A summary of the Amended EIM® strategy can be found in Figure 11.

It has been shown that the PAVS questionnaire can be integrated into the electronic medical record system of a large healthcare system (Coleman et al., 2012), a strategy that can likely be used for the implementation of the PAR-Q, as well. It is recommended that both of these tools be implemented into the electronic medical records systems in all hospitals and clinics. In this way, primary care staff will be forced to “check the boxes” of the PAVS and PAR-Q during all routine check-ups, in the same way that patient weight is recorded and blood pressure taken before an examination. This addition to regular tasks will realistically take no more than one to two minutes of total staff time, as these tests are comprised of a combined 9, short answer (less than three words), questions. This amendment accomplishes the task of monitoring patient physical activity levels and ensuring safe participation. It also serves to reduce the time commitment of primary care personnel.

Physical activity behavior change counseling strategies have not been demonstrated to be effective in the clinical setting (AuYoung et al., 2016; Eden et al., 2002). Of concern in the literature, is the intervention intensity, or number and duration of meetings between doctor and patient, required to elicit a meaningful change in behavior (Grossmann et al., 2010). For example, a systematic review and meta-analysis of physical activity interventions utilizing strategies aimed at changing self-efficacy, the underlying principle of the Exercise Stages of Change model, found a small but significant effect ($d = 0.16$, $p < 0.001$) of interventions on self-efficacy (Ashford, Edmunds, & French, 2010). However, 75% of the reviewed studies lasted six or more weeks and 60% of the reviewed studies included six or more sessions. Meanwhile, primary care practitioners, in an unsolicited email response to a recent survey, suggested that the current EIM® strategy be amended to call for only once annual implementation. This evidence demonstrates that even small effects on self-efficacy require relatively high-intensity behavior counseling strategies, the likes of which, primary care practitioners are unwilling to undertake. For these reasons it is recommended that this step be removed, in order to lessen the burden placed on the primary care practitioner.

Although handwritten prescriptions have been demonstrated as being superior to verbal advice alone in affecting physical activity behavior, primary care practitioners do not agree or disagree that it is within their scope of practice to write them (Rourk, Olson, et al., 2018). Again, the unwillingness of primary care practitioners to participate in a step of the EIM® process must be taken into account, as these practitioners are not required or incentivized to cooperate in any meaningful way. By including steps that are viewed by practitioners as outside of the scope of their practice, a prospective practitioner is likely to "throw the baby out with the bathwater" and disregard all of the steps of the 5-step EIM® process entirely. It is recommended that this step be either removed completely, or made optional, so as not to alienate practitioners that feel that it is not within their scope of practice.

The primary focus of the Amended EIM® strategy should be directed at the development of an exercise professional referral network. This network must be trusted, effective and easy to use by practitioners and patients alike. When surveyed, primary care practitioners agreed that this step was within their scope of practice more than any other (Rourk, Olson, et al., 2018). However, 91.34% of the same practitioners referred less than 20% of their patients to exercise professionals, and 45.19% never referred patients. This evidence demonstrates that primary care practitioners are in favor of referring patients to exercise professionals, but not willing to take the necessary steps to actually execute such a behavior. The EIM® seemed to be prepared for this barrier as evidenced by the length of the section in the Healthcare Providers' Action Guide (American College of Sports Medicine, 2016) detailing how a primary care practitioner could go about developing a network of exercise professionals, to whom they could refer. In keeping with the strategy of reducing the time-related burden on practitioners, the steps required to develop and use a network of exercise professionals must be accomplished by a third party. In this case, it is recommended that the ACSM and EIM® be that third party.

A secondary focus should be increasing visibility and awareness of the new Amended EIM® model. The finding that 68.27% of primary care practitioners have never heard of EIM® is unacceptable. Considerable resources need to be invested into increasing the visibility of the Amended EIM® strategy. Primary care practitioners need to be made aware of their responsibilities, the PAVS and PAR-Q questionnaires need to be required within the electronic medical record systems of all hospitals and clinics, and an easy to use and effective network of exercise professionals must be made readily available to practitioners and patients alike.

Lastly, a system of surveillance dedicated to measuring outcomes related to the implementation of the EIM® will provide information useful for future amendments. Over a decade has passed since the inception of the EIM® and this is the first critical analysis to date. In the future, higher standards of accountability and measures of efficacy should be required to ensure efficient and effective implementation of the amended strategy.

Conclusion

The current version of the EIM® strategy relies too heavily upon the primary care practitioner. Of chief concern are the lack of perceived time available and the lack of support for the current strategy, by the primary care practitioner. After reviewing the evidence, it appears that the primary practitioner is well positioned to execute only a portion of the current 5-step EIM® strategy. We suggest that the ACSM EIM® initiative focus on soliciting primary care practitioners to assess patient physical activity levels and ability by imbedding the PAVS and APR-Q into the electronic medical records systems of hospitals and clinics nationwide. Upon assessment, practitioners should then refer patients to appropriate exercise and medical professionals found within a newly developed exercise professional referral network. Development of this referral network and pathway should be the responsibility of the EIM® planners, as not to burden practitioners. Increasing visibility and awareness of the Amended EIM® strategy, should become a major focus of the EIM® as well. Lastly, a system of surveillance dedicated to monitoring the implementation and efficacy of the EIM® strategy should be put in place, in order to provide planners with information as to optimize the strategy over time.

Chapter 6.

Overall Conclusions and Future Directions

Increased population physical activity has the potential to significantly impact both the healthcare system as a whole as well as individual well-being. The economic analysis presented in this dissertation, provides insight into the scope of this effect. Total diagnosed clinical cases of cardiovascular disease, stroke, type II diabetes mellitus, Alzheimer's disease, breast cancer, colon cancer and depression attributable to physical inactivity are estimated at between 19 and 28 million and total direct medical costs attributable to physical inactivity are estimated between USD 109 and 155 billion, annually. These costs represent between 3.3 and 4.7% of total annual direct medical spending in the United States. Clinicians and policymakers alike can expect a reduction in diagnosed cases of over a quarter of a million and savings in direct medical costs of over USD 1 billion, for every 0.96 absolute percentage point change in the proportion of individuals that meet the weekly exercise recommendations.

These clinical and economic benefits provide a rationale for the implementation of a population level intervention directed at increasing the proportion of Americans that meet the weekly physical activity recommendations. One such intervention currently exists, the ACSM EIM® initiative. The proposed strategy by the EIM® relies heavily on the implementation of a 5-step process by primary care practitioners. Little research has been performed to investigate whether or not this proposed strategy has been implemented or made effective in practice, since its inception in 2007.

The survey of primary care practitioner's knowledge and understanding of the EIM®, presented in this dissertation demonstrate that primary care providers are unaware of the EIM® initiative and its 5-step process, do not currently implement the steps of the process, and do not believe that said implementation is within their scope of practice. These findings combined with the integral nature of the primary care practitioner within the proposed EIM® strategy, warrant a critical review of the current EIM® strategy. The current EIM® strategy places too many demands on primary care practitioners. Further, individually, the steps of the current EIM® strategy have never been shown to affect physical activity behavior. For these reasons it is recommended that the current EIM® strategy be amended. The PAVS and PAR-Q should be required in the electronic medical record systems of all hospitals and clinics, and primary care physicians should refer patients to exercise professionals when deemed necessary. To facilitate the referral of patients to exercise professionals, the ACSM EIM® planners should invest a bulk of their resources in to the development of a referral network that is easy to use for both practitioners and patients alike. The lack of such a network is likely a barrier to the implementation of the referral process, as a majority of practitioners agree that they should be referring patients to exercise professionals, however, very few actually are. Lastly, the EIM® must invest considerable effort and resources into visibility.

The primary future directive stemming from this dissertation is the development of a feasible and effective exercise professional referral network. Future study is required to determine the necessary components for such a network as well as to ascertain and overcome the logistical aspects of its implementation.

Secondarily, efforts need to be made to increase the visibility of the Amended EIM® strategy outside of exercise professionals, with special focus on primary care practitioners. Without awareness and understanding no proposed strategy will work.

Thirdly, continual surveillance of outcomes related to the amended EIM® model are warranted. This dissertation is the first attempt in over a decade to assess the efficacy of the EIM® model. A system of surveillance is necessary to provide planners and decision makers with data helpful in optimizing the future direction of the strategy.

References

Adams, V., Lenk, K., Linke, A., Lenz, D., Erbs, S., Sandri, M., … Hambrecht, R. (2004). Increase of circulating endothelial progenitor cells in patients with coronary artery disease after exercise-induced ischemia. *Arterioscler Thromb Vasc Biol*, *24*, 684–690.

Ahlskog, J. E., Geda, Y. E., Graff-radford, N. R., & Petersen, R. C. (2011). Physical Exercise as a Preventive or Disease-Modifying Treatment of Dementia and Brain Aging. *Mayo Clinic Proceedings*, *55905*(9), 876–884. http://doi.org/10.4065/mcp.2011.0252

Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (2007). International Diabetes Federation : a consensus on Type 2 diabetes prevention. *Diabetic Medicine*, 451–463. http://doi.org/10.1111/j.1464-5491.2007.02157.x

Albright, A., Franz, M., & Hornsby, G. (2000). American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Medical Science in Sports and Exercise*, *32*(7), 1345–1360.

Alzheimer's Association. (2015). Alzheimer's Association Report 2015 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *11*(3), 332–384. http://doi.org/10.1016/j.jalz.2015.02.003

American College of Sports Medicine. (2016). Exercise is Medicine Healthcare Providers ' Action Guide. *American College of Sports Medicine (ACSM)*, *5*(3), 1–25.

American Diabetes Association. (2014). Standards of Medical Care in Diabetes- 2014. *Diabetes Care*, *37*(January), 14–80. http://doi.org/10.2337/dc14-S014

American Heart Association. (2014). American Heart Association Recommendations for

Physical Activity in Adults. Retrieved from https://www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-Activity-in-Adults_UCM_307976_Article.jsp?appName=WebApp

Andersen, P., & Henriksson, J. (1977). Training induced changes in the subgroups of human type II skeletal muscle fibres. *Acta Physiol Scand*, *99*, 123–5.

Andersen, P., & Saltin, B. (1985). MAXIMAL PERFUSION OF SKELETAL MUSCLE IN MAN. *Journal of Physiology*, 233–249.

Arena, R., Myers, J., & Guazzi, M. (2008). The Clinical Significance of Aerobic Exercise Testing and Prescription : From Apparently Healthy to Confirmed Cardiovascular Disease. *American Journal of Lifestyle Medicine*, *2*(6). http://doi.org/10.1177/1559827608323210.

Asahara, T., Takahashi, T., & Masuda, H. (1999). VEGF contributes to postnatal neovascularization by mobilizing bone-marrow endothelial progenitor cells. *EMBO Journal*, *18*, 3964–3972.

Ashford, S., Edmunds, J., & French, D. P. (2010). What is the best way to change self-efficacy to promote lifestyle and recreational physical activity? A systematic review with meta-analysis. *British Journal of Health Psychology*, *15*(2), 265–288. http://doi.org/10.1348/135910709X461752

Askari, A., Unzek, S., Popovic, Z., Goldman, C., Forudi, F., Kiedrowski, M., … Penn, M. (2003). Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet*, *362*, 697–703.

Aune, D., Norat, T., Leitzmann, M., Tonstad, S., & Vatten, L. J. (2015). Physical activity and the risk of type 2 diabetes : a systematic review and dose – response meta-analysis. *European Journal of Epidemiology*, *30*(7), 529–542. http://doi.org/10.1007/s10654-015-0056-z

AuYoung, M., Linke, S. E., Pagoto, S., Buman, M. P., Craft, L. L., Richardson, C. R., … Sheinfeld Gorin, S. (2016). Integrating Physical Activity in Primary Care Practice. *American Journal of Medicine*, *129*(10), 1022–1029. http://doi.org/10.1016/j.amjmed.2016.02.008

Baggish, A. L., Yared, K., Wang, F., Weiner, R. B., Jr, A. M. H., Picard, M. H., & Wood, M. J. (2008). The impact of endurance exercise training on left ventricular systolic mechanics. *American Journal of Physiology*, *295*, 1109–1116. http://doi.org/10.1152/ajpheart.00395.2008.

Barnes, D. E., & Yaff, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet*, *10*, 819–828. http://doi.org/10.1016/S1474-4422(11)70072-2

Barnes, P. M., & Schoenborn, C. (2012). Trends in adults receiving a recommendation for exercise or other physical activity from a physician or other health professional. *NCHS Data Brief*, (86), 1–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22617014

Bertagnoli, M., Eagle, C., Zauber, A., Redston, M., Solomon, S. D., Kim, K., … Hawk, E. T. (2006). Celecoxib for the Prevention of Sporadic Colorectal Adenomas. *The New England Journal of Medicine*, *355*(9), 873–884.

Bertagnolli, M. M., Eagle, C. J., Zauber, A. G., Redston, M., Breazna, A., Kim, K., … Hawk, E. T. (2009). Five-Year Efficacy and Safety Analysis of the Adenoma Prevention with Celecoxib Trial. *Cancer Prevention Research*, *2*(April), 310–322. http://doi.org/10.1158/1940-6207.CAPR-08-0206

Bjorntop, P. (1991). Metabolic implications of body fat distribution. *Diabetes Care*, *14*, 1132–1143.

Blondell, S. J., Hammersley-mather, R., & Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC Public Health*, *14*(510), 1–12.

Blood Pressure Lowering Treatment Trialists' Collaboration. (2003). Effects of different blood-pressure-lowering regimens on major cardiovascular events : results of prospectively-designed overviews of randomised trials. *The Lancet*, *362*, 1527–1535.

Blood Pressure Lowering Treatment Trialists' Collaboration. (2008). Effects of Different Regimens to Lower Blood Pressure on Major Cardiovascular Events in Older and Younger People : Meta-Analysis of Randomised Trials. *British Medical Journal*, *336*(7653), 1121–1123. http://doi.org/10.1136/bmj.39548.738368.BE

Blumenthal, J., Babyak, M., Doraiswamy, M., Watkins, L., Hoffman, B., Barbour, K., … Sherwood, A. (2007). Exercise and Pharmacotherapy in the Treatment of Major Depressive Disorder. *Psychosomatic Medicine*, *69*, 587–596. http://doi.org/10.1097/PSY.0b013e318148c19a

Boer, M. C. De, Wörner, E. A., Verlaan, D., & Leeuwen, P. A. M. Van. (2017). The

Mechanisms and Effects of Physical Activity on Breast Cancer. *Clinical Breast Cancer*, 1–7. http://doi.org/10.1016/j.clbc.2017.01.006

Bouassida, A., Chamari, K., Zaouali, M., Feki, Y., Zbidi, A., & Tabka, Z. (2010). Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. *British Journal of Sports Medicine*, *44*, 620–630.

Bowles, D. K., & Laughlin, M. H. (2011). Mechanism of beneficial effects of physical activity on atherosclerosis and coronary heart disease. *Journal of Applied Physiology*, *111*, 308–310. http://doi.org/10.1152/japplphysiol.00634.2011.Mechanism

Buchanan, C., & Marsh, R. (2002). Effects of exercise on the biomechanical, biochemical and structural properties of tendons. *Comparative Biochemistry and Physiology*, *133*(1101–1107).

Burr, J. F., Rowan, C. P., Jamnik, V. K., & Riddell, M. C. (2010). The Role of Physical Activity in Type 2 Diabetes Prevention : Physiological and Practical Perspectives. *The Physician and Sports Medicine*, *38*(1), 72–82.

Carmeliet, P. (2000). Mechanisms of angiogenesis and arteriogenesis. *Nature*, *6*(3), 389–395.

Caspersen, C. J., Powell, K. E., Christenson, G. M., Public, S., Reports, H., Apr, N. M., & Reports, P. H. (1985). Physical Activity , Exercise , and Physical Fitness : Definitions and Distinctions for Health- Related Research. *Association of Schools of Public Health*, *100*(2), 126–131. Retrieved from http://www.jstor.org/stable/20056429

Cauza, E., Hanusch-Enserer, U., & Strasser, B. (2005). The relative benefits of endurance and strength training on the metabolic factor and muscle function of people with type 2 diabetes mellitus. *Archives of Physical Medicine and Rehabilitation*, *86*(8), 1527–1533.

Center for Behavioral Health Statistics and Quality. (2016). 2015 National Survey on Drug Use and Health : Detailed Tables. *2015 National Survey on Drug Use and Health*, 209. Retrieved from http://www.samhsa.gov/data/population-data-nsduh/reports?tab=38

Centers For Medicare and Medicaid Services. (2016). National Health Expenditure Fact Sheet.

Chan, A. T., & Giovannucci, E. L. (2010). Primary Prevention of Colorectal Cancer. *Gastroenterology*, *138*(6), 2029–2043. http://doi.org/10.1053/j.gastro.2010.01.057

Chan, A. T., Giovannucci, E. L., Meyerhardt, J. A., Schernhammer, E. S., Curhan, G. C., & Fuchs, C. S. (2006). Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer. *JAMA*, *294*(8), 914–923.

Chan, A. T., Giovannucci, E. L., Meyerhardt, J. A., Schernhammer, E. S., Wu, K., & Fuchs, C. S. (2008). Aspirin Dose and Duration of Use and Risk of Colorectal Cancer in Men. *Gastroenterology*, *134*(1), 21–28. http://doi.org/10.1053/j.gastro.2007.09.035.ASPIRIN

Chan, M. F. (2007). Usual physical activity and endogenous sex hormones in postmenopausal women: the European prospective investigation into cancer — Norfolk population study. *Cancer Epidemiol. Biomarkers Prev, 16*, 900–905.

Chen, W., Zhang, X., & Huang, W. J. (2016). Role of physical exercise in Alzheimer's disease (Review). *Biomedical Reports*, 403–407. http://doi.org/10.3892/br.2016.607

Cheng, S., & Kujala, U. M. (2012). Exercise in type 2 diabetes : The mechanisms of resistance and endurance training. *Journal of Sport and Health Science*, *1*, 65–66. http://doi.org/10.1016/j.jshs.2012.05.002

Coggan, A., Kohrt, W., & Spina, R. (1990). Endurance training decreases plasma glucose turnover and oxidation during moderate intensity exercise in men. *Journal of Applied Physiology*, *68*, 990–6.

Colberg, S., Sigal, R., Fernhall, B., Regensteiner, J., Blissmer, B., Rubin, R., … Braun, B. (2010). Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*, *33*(12). http://doi.org/10.2337/dc10-9990

Colberg, S., Sigal, R., Yardley, J., Riddell, M., Dunstan, D., Dempsey, P., … Tate, D. (2016). Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care*, *39*, 2065–2079.

Colditz, G. A. (1999). Economic costs of obesity and inactivity. *Medicine & Science in Sports & Exercise*, *31*(11), S663.

Cole, B. F., Logan, R. F., Halabi, S., Benamouzig, R., Sandler, R. S., Grainge, J., … Baron, J. A. (2009). Aspirin for the Chemoprevention of Colorectal Adenomas : Meta-analysis of the Randomized Trials. *Journal Od the NAtional Cancer Institue*, *101*, 256–266. http://doi.org/10.1093/jnci/djn485

Coleman, K. J., Ngor, E., Reynolds, K., Quinn, V. P., Koebnick, C., Young, D. R., …

Sallis, R. E. (2012). Initial validation of an exercise “vital sign” in electronic medical records. *Medicine and Science in Sports and Exercise*, *44*(11), 2071–2076. http://doi.org/10.1249/MSS.0b013e3182630ec1

Cook, N. R., Lee, I., Gaziano, J. M., Gordon, D., Ridker, P. M., Manson, J. E., … Buring, J. E. (2005). Low-Dose Aspirin in the Primary Prevention of Cancer The Women’s Health Study: A Randomized Controlled Trial Nancy. *Jama*, *294*(1), 47–55.

Corcoran, M., Lamon-Fava, S., & Fielding, R. (2007). Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. *American Journal of Clinical Nutrition*, *85*(3), 662–677.

Cornelissen, A., Buys, R., & Smart, N. A. (2013). Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis. *Journal of Hyperten*, *31*, 639–648. http://doi.org/10.1097/HJH.0b013e32835ca964

Cornelissen, A., & Fagard, R. H. (2005). Effects of Endurance Training on Blood Pressure , Blood Pressure – Regulating Mechanisms , and Cardiovascular Risk Factors. *Hypertension*, *46*, 667–675. http://doi.org/10.1161/01.HYP.0000184225.05629.51

Dawson, E., Green, D., Cable, N., & Thijssen, D. (1985). Effects of acute exercise on flow-mediated dilatation in healthy humans. *Journal of Applied Physiology*, *115*, 1589–1598.

de Salles, B., Simao, R., Fleck, S., Dias, I., & Kraemer-Aguiar, LG Bouskela, E. (2010). Effects of resistance training on cytokines. *International Journal of Sports Medicine*, *31*, 441–450.

de Winter, J. C. F., & Dodou, D. (2010). Five-Point Likert Items : t test versus Mann-Whitney-Wilcoxon. *Practical Assessment, Research & Evaluation*, *15*(11), 1–16. http://doi.org/citeulike-article-id:10781922

DeFronzo, R., & Tripathy, D. (2009). Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*, *32*, 157–163.

Dempsey, J. (1985). Is the lung built for exercise? *Medicina and Science in Sport and Exercise*.

Dempsey, J., & Wagner, P. (1999). Exercise-induced arterial hypoxemia. *Journal of Applied Physiology*, 1997–2006.

Despres, J.-P., Nadeau, A., & Bouchard, C. (1988). Physical training and changes in regional adipose tissue distribution. *Acta Med Scand Suppl*, *723*, 205–212.

Diep, L., Kwagyan, J., Kurantsin-Mills, J., Weir, R., & Jayam-Trouth, A. (2010). Association of Physical Activity Level and Stroke Outcomes in Men and Women : A Meta-Analysis. *Journal of Women's Health*, *19*(10).

Ding, D., Lawson, K. D., Kolbe-Alexander, T. L., Finkelstein, E. A., Katzmarzyk, P. T., van Mechelen, W., & Pratt, M. (2016). The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *The Lancet*, *388*(10051), 1311–1324. http://doi.org/10.1016/S0140-6736(16)30383-X

Diniz, B., Pinto, J., Guimares, M., Gattaz, W., & Forlenza, O. (2009). To treat or not to treat ? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer ' s disease. *European Archive of Psychiatry and Clinical Neuroscience*, *259*, 248–256. http://doi.org/10.1007/s00406-

008-0864-1

Dubois, B., Feldman, H., Jacova, C., Cummings, J., Dekosky, S., Barberger-Gateau, P., … Galasko, D. (2010). Revising the definition of Alzheimer's disease. *Lancet Neurology*, *9*, 1118–1127.

Eden, K. B., Orleans, C. T., Mulrow, C. D., Pender, N. J., & Teutsch, S. M. (2002). Clinical Guidelines Does Counseling by Clinicians Improve Physical Activity ? A Summary. *Annals of Internal Medicine*, *137*(3), 208–215. http://doi.org/10.7326/0003-4819-137-3-200208060-00015

Egan, B., & Zierath, J. R. (2012). Review Exercise Metabolism and the Molecular Regulation of Skeletal Muscle Adaptation. *Cell Metabolism*, *17*(2), 162–184. http://doi.org/10.1016/j.cmet.2012.12.012

Eriksen, M., Mackay, J., Schluger, N., Gomeshtapeh, F. I., & Drope, J. (2015). *The Tobacco Atlas: 5th edition*.

Fagard, R. H., & Cornelissen, A. (2007). Effect of exercise on blood pressure control in hypertensive patients. *European Society of Cardiology*, *14*, 12–17.

Ferrara, C., Goldberg, A., Ortmeyer, H., & Ryan, A. (2006). Effects of aeribc and resistive exercise training on glucose disposal and skeletal muscle metabolism in older men. *J Gerontol A Biol Sci Med Sci*, *61*(5), 480–487.

Figurov, A., Pozzo-Miller, L. D., Olafsson, P., Wang, T., & Lu, B. (1996). Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature*, *381*, 706–709.

Fisher, B., Costantino, J. P., Wickerham, D. L., Carol, K., Kavanah, M., Cronin, W. M.,

… Wolmark, N. (1998). Tamoxifen for Prevention of Breast Cancer : Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute*, *90*(18).

Fisslthaler, B., Dimmeler, S., Hermann, C., Busse, R., & Fleming, I. (2000). Phosphorylation and activation of the endothelial nitric oxide synthase by fluid shear stress. *Acta Physiol Scand*, *168*, 81–88.

Flossmann, E., & Rothwell, P. M. (2007). Effect of aspirin on long-term risk of colorectal cancer : consistent evidence from randomised and observational studies. *The Lancet*, *369*, 1603–1613.

Fountoulakis, K. N., & Moller, H.-J. (2011). Efficacy of antidepressants : a re-analysis and re-interpretation of the Kirsch data. *Internatioanl Journal of Neuropsychopharmacology*, *14*, 405–412. http://doi.org/10.1017/S1461145710000957

Freedman, A. N., Yu, B., Gail, M. H., Costantino, J. P., Graubard, B. I., Vogel, V. G., … Mccaskill-stevens, W. (2011). Benefit / Risk Assessment for Breast Cancer Chemoprevention With Raloxifene or Tamoxifen for Women Age 50 Years or Older. *Journal of Clinical*, *29*(17), 2327–2333. http://doi.org/10.1200/JCO.2010.33.0258

Gann, P. H., Joann, E., Glynn, R. J., Buring, J. E., & Hennekens, C. H. (1993). Low-Dose Aspirin and Incidence of Colorectal Tumors in a Randomized Trial. *Journal of the National Cancer Institute*, *85*(15).

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.

M., … Swain, D. P. (2011). Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Medicine and Science in Sports and Exercise*, *43*(7), 1334–1359. http://doi.org/10.1249/MSS.0b013e318213fefb

Garrett, N. A., Brasure, M., Schmitz, K. H., Schultz, M. M., & Huber, M. R. (2004). Physical inactivity: Direct cost to a health plan. *American Journal of Preventive Medicine*, *27*(4), 304–309. http://doi.org/10.1016/j.amepre.2004.07.014

Gascon, F., Valle, M., & Martos, R. (2000). Sex hormone-binding globulin as a marker for hyperinsulinemia and/or insulin resistance in obese children. *European Journal of Endocrinology*, *143*, 85–89.

Gaster, M., Vach, W., Beck-Nielsen, H., & Schroder, H. (2002). GLUT4 expression at the plasma membrane is related to fibre volume in human skeletal muscle fibres. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica*, *110*(9), 611–619.

Geldmacher, D. (2003). Long-Term Cholinesterase Inhibitor Therapy for Alzheimer's Disease: Practical Considerations for the Primary Care Physician. *Primary Care Companion J Clin Psychiatry*, *5*(6), 251–259.

Gibala, M. J., Lean, D. A. M. A. C., Graham, T. E., Saltin, B., Martin, J., Maclean, D. A., … Saltin, B. (1998). Tricarboxylic acid cycle intermediate pool size and estimated cycle flux in human muscle during exercise. *American Journal of Physiology*, *275*(12), 235–242.

Gillies, C., Abrams, K., Lambert, Pa., Cooper, N., Sutton, A., Hsu, R., & Khunti, K.

(2007). Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance : systematic review and meta-analysis. *British Medical Journal*, *55*(January). http://doi.org/10.1136/bmj.39063.689375.55

Glanz, K., Rimer, B., & Viswanath, K. (2008). *Health Behavior and Health Education*.

Gledhill, N., Cox, D., & Jamnik, R. (1994). Endurance athletes' stroke volume does not plateau: Major advantage is diastolic function. *Medicine & Science in Sports & Exercise*, *26*, 1116–1121.

Gleeson, M., Bishop, N., Stensel, D., Lindley, M., Mastana, S., & Nimmo, M. (2011). The anti- inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*, *11*, 607–615.

Golightly, Y. M., Allen, K. D., Ambrose, K. R., Stiller, J. L., Evenson, K. R., Voisin, C., … Callahan, L. F. (2017). Physical Activity as a Vital Sign: A Systematic Review. *Preventing Chronic Disease*, *14*, 170030. http://doi.org/10.5888/pcd14.170030

Gomez-Pinilla, F., So, V., & Kesslak, J. P. (2001). Spatial learning induces neurotrophin receptor and synapsin I in the hippocampus. *Brain Research*, *904*, 13–19.

González, K., Fuentes, J., & Márquez, J. L. (2017). Physical Inactivity , Sedentary Behavior and Chronic Diseases. *Korean Journal of Family Medicine*, *38*, 111–115.

Goto, C., Higashi, Y., Kimura, M., Noma, K., Hara, K., Nakagawa, K., … Nara, I. (2003). Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation, 108*, 530–535.

Graf, C., & Wessely, N. (2010). Breast Care Physical Activity in the Prevention and Therapy of Breast Cancer. *Breast Care*, *5*, 389–394. http://doi.org/10.1159/000322650

Grant, R. W., Schmittdiel, J. A., Neugebauer, R. S., Uratsu, C. S., & Sternfeld, B. (2014). Exercise as a vital sign: A quasi-experimental analysis of a health system intervention to collect patient-reported exercise levels. *Journal of General Internal Medicine*, *29*(2), 341–348. http://doi.org/10.1007/s11606-013-2693-9

Green, H., Jones, S., & Ball-Burnett, M. (1995). Adaptations inmuscle metabolism to prolonged voluntary exercise and training. *Journal of Applied Physiology1*, *78*, 138–45.

Green, H., Smith, D., & Murphy, P. (1990). Training-induced alterations in muscle glycogen utilisation in fibre-specific types during prolonged exercise. *Canadian Journal of Physiology and Pahrmacology*, *68*, 1372–6.

Greenberg, P. E., Fournier, A., Sisitsky, T., Pike, C. T., & Kessler, R. C. (2015). The Economic Burden of Adults With Major Depressive Disorder in the United States (2005 and 2010). *Journal of Clinical Psychiatry*, *76*(2), 155–162. http://doi.org/10.4088/JCP.14m09298

Grossmann, M., Ray, A., & Nkhata, K. (2010). Obesity and breast cancer: status of leptin and adiponectin in pathological processes. *Cancer Metastasis Rev*, *29*, 641–653.

Guadalupe-Grau, A., Fuentes, T., Guerra, B., & Calbet, J. (2009). Exercise and Bone Mass in Adults. *Sports Medicine*, *39*(6), 439–468.

Hagberg, J., & Brown, M. (1995). Does exercise training play a role in the treatment of essential hypertension? *Journal of Cardiovascular Risk*, *2*, 296–302.

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease : a systematic review of prospective evidence. *Psychological Medicine*, *39*, 3–11. http://doi.org/10.1017/S0033291708003681

Harms, S., & Hickson, R. (1983). Skeletal muscle mitochondria andmyoglobin, endurance, and intensity of training. *Journal of Applied Physiology*, *54*, 798–802.

Harris, H., Tworoger, S., Hankinson, S., Rosner, B., & Michels, K. (2011). Plasma leptin levels and risk of breast cancer in premenopausal women. *Cancer Prev Res*, *4*, 1449–1456.

Haskell, W. L., Lee, I., Pate, R. R., Powell, K. E., & Blair, S. N. (2007). Physical Activity and Public Health : Updated Recommendation for Adults From the American College of Sports Medicine and the American Heart Association. *Circulation*, *116*(9), 1423–1434. http://doi.org/10.1249/mss.0b013e3180616b27

Heaps, C. L., & Parker, J. L. (2011). Effects of exercise training on coronary collateralization and control of collateral resistance. *Journal of Applied Physiology*, *111*, 587–598. http://doi.org/10.1152/japplphysiol.00338.2011.

Heeschen, C., Aicher, A., Lehmann, R., Fichtlscherer, S., Vasa, M., Urbich, C., … Dimmeler, S. (2003). Erythropoietin is a potent physiological stimulus for endothelial progenitor cell mobilization. *Blood*, *102*, 1340–1346.

Heil, M., Eitenmuller, I., Schmitz-Rixen, T., & Schaper, W. (2006). Arteriogenesis versus angiogenesis: similarities and differences. *JCMM*, *10*(1), 45–55.

Henriksson, J., & Reitman, J. (1977). Time course of changes in human skeletal muscle succinate dehydrogenase and cytochrome oxidase activities and maximal oxygen uptake with physical activity and inactivity. *Acta Physiol Scand*, *99*, 91–97.

Higashida, K., Kim, S., Higuchi, M., Holloszy, J., & Han, D. (2011). Normal adaptations to exercise despite protection against oxidative stress. *American Journal of Physiology Endocrinology and Metabolism*, *301*, 779–784.

Holloszy, J. (1973). Biochemical adaptations to exercise: aerobic metabolism. *Exercise and Sport Sciences Reviews*, 45–71.

Holloszy, J. (2008). Regulation by exercise of skeletal muscle content of mitochondria and GLUT4. *Journal of Physiology and Pharmacology*, *59*, 5–18.

Holloszy, J., & Coyle, E. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *Journal of Applied Physiology*, *56*, 831–838.

Holten, M., Zacho, M., Gaster, M., Juel, C., Wojtaszewski, J., & Dela, F. (2004). Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. *Diabetes*, *53*(2), 294–305.

Howald, H., Hoppeler, H., Claassen, H., Mathieu, O., & Straub, R. (1985). Influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans. *European Journal of Physiology*, 369–376.

Hughes, V., Fiatarone, M., & Fielding, R. (1993). Exercise increases muslce GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. *American Journal of Physiology*, *264*, 855–862.

Huijg, J. M., Gebhardt, W. A., Verheijden, M. W., van der Zouwe, N., de Vries, J. D., Middelkoop, B. J. C., & Crone, M. R. (2015). Factors Influencing Primary Health Care Professionals' Physical Activity Promotion Behaviors: A Systematic Review. *International Journal of Behavioral Medicine*, *22*(1), 32–50. http://doi.org/10.1007/s12529-014-9398-2

Hurley, B., Nemeth, P., & Martin, W. (1986). Muscle triglyceride utilisation during exercise: effect of training. *Journal of Applied Physiology*, *60*, 562–7.

Il'yasova, D. (2005). Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol. Biomarkers Prev.*, *14*, 2413–2418.

Ingjer, F. (1979). Effects of endurance training on muscle fibre ATPase activity, capillary supply and mitochondrial content in man. *Journal of Physiology*, *294*, 419–32.

Interagency Breast Cancer and Environmental Research Coordinating Committee. (2013). *Breast Cancer and the Environment. Prioritizing Prevention*.

Issurin, V. (2010). New Horizons for the Methodology and Physiology of Training Periodization. *Sports Medicine*, *40*(3), 189–206.

Ivy, J. L. (1997). Role of Exercise Training in the Prevention and Treatment of Insulin Resistance and Non-Insulin-Dependent Diabetes Mellitus. *Sports Medicine*, *24*(5), 321–336.

Iwakura, A., Shastry, S., Luedemann, C., Hamada, H., Kawamoto, A., Kishore, R., … Asahara T, L. D. (2006). Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix m. *Circulation*, *113*, 1605–1614.

Jarde, T., Caldefie-Chezet, F., & Goncalves-Mendes, N. (2009). Involvement of adiponectin and leptin in breast cancer: clinical and in vitro studies. *Endocr Relat Cancer*, *16*, 1197–1210.

Jennings, G., Deakin, G., Korner, P., Meredith, I., Kingwell, B., & Nelson, L. (1991). What is the dose-response relationship between exercise training and blood pressure? *Annals of Internal Medicine*, *23*, 313–318.

Jeon, C., Hu, F., Lokken, R. P., Dam, V., & M., R. (2007). Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes. *Diabetes Care*, *30*. http://doi.org/10.2337/dc06-1842

Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B., & Berry, D. A. (2013). Meta-analyses of colorectal cancer risk factors. *Cancer Causes and Control*, *24*, 1207–1222. http://doi.org/10.1007/s10552-013-0201-5

Jones, A. M., & Carter, H. (2000). The Effect of Endurance Training on Parameters of Aerobic Fitness. *Sports Medicine*, *29*(6), 373–386.

Josefsson, T., Lindwall, M., & Archer, T. (2014). Physical exercise intervention in depressive disorders : Meta-analysis and systematic review. *Scandinavian Journal of Medicine and Science in Sports*, *24*, 259–272. http://doi.org/10.1111/sms.12050

Kaaks, R., & Lukanova, A. (2001). Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc. Nutr. Soc.*, *60*, 91–106.

Kang, H., Welcher, A. A., Shelton, D., & Schuman, E. M. (1997). Neurotrophins and time: different roles for TrkB signaling in hippocampal long-term potentiation.

Neuron, *19*, 653–664.

Katzmarzyk, P. T., Gledhill, N., & Shephard, R. J. (2000). The economic burden of physical inactivity in Canada. *Canadian Medical Association Journal*, *163*(11), 1435–1440.

Kelley, G. A., Kelley, K. A., & Tran, Z. V. (2001). Aerobic Exercise and Resting Blood Pressure : A Meta-Analytic Review of Randomized , Controlled Trials. *Preventative Cardiology*, 73–80.

Kenney, M., & Seals, D. (1993). Postexercise hypotension: key features, mechanisms, and clinical significance. *Hypertesion*, *22*, 653–664.

Key, T., Appleby, P., Barnes, P., & Reeves, G. (2002). The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *Journal of National Cancer Institute*, *94*, 606–616.

Kiens, B., & Essen-Gustavsson, B Christensen, N. (1993). Skeletal strate utilisation during sub-maximal exercise in man: effect of endurance training. *Journal of Physiology*, *469*(459–78).

Kirsch, I., Deacon, B. J., Huedo-medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial Severity and Antidepressant Benefits : A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLOS Medicine*, *5*(2). http://doi.org/10.1371/journal.pmed.0050045

Klausen, K., Andersen, L., & Pelle, I. (1981). Adaptive changes in work capacity, skeletal muscle capillirization and enzyme levels during training and detraining.

Acta Physiol Scand, *113*, 9–16.

Korte, M., Carroll, P., Wolf, E., Brem, G., Thoenen, H., & Bonhoeffer, T. (1995). Hippocampal long-term potentiation is impaired in mice lacking brainderived neurotrophic factor. *Proc. Natl. Acad. Sci.*, *92*(8856–8860).

Kubo, K., Kanehisa, H., Kawakami, Y., & Fukunaga, T. (2000). Elastic properties of muscle-tendon complex in long-distance runners. *European Journal of Applied Physiology*, *81*, 181–187.

Kushi, L., Doyle, C., McCullough, M., Rock, C., Demark-Wahnefried, W., Bandera, E., … Gansler, T. (2012). American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity. *American Cancer Society*. http://doi.org/10.3322/caac.20140.Available

Kyu, H. H., Bachman, V. F., Alexander, L. T., Mumford, J. E., Afshin, A., Estep, K., … Forouzanfar, M. H. (2016). Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events : systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *The British Medical Journal*, *354*(3857), 1–10. http://doi.org/10.1136/bmj.i3857

Lago, R. M., Singh, P. P., & Nesto, R. W. (2007). Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones : a meta-analysis of randomised clinical trials. *The Lancet*, *370*, 1129–1136.

Lange-asschenfeldt, C., & Kojda, G. (2008). Alzheimer ’ s disease , cerebrovascular dysfunction and the benefits of exercise : From vessels to neurons. *Experimental Gerontology*, *43*, 499–504. http://doi.org/10.1016/j.exger.2008.04.002

Laufs, U., Werner, N., Link, A., Endres, M., Wassmann, S., Jürgens, K., … Nickenig, G. (2004). Physical training increases endothelial progenitor cells, inhibition of neointima formation, and enhances angiogenesis. *Circulation*, *109*, 220–226.

Laughlin, M., & Roseguini, B. (2008). Mechanisms for exercise training-induced increases in skeletal muscle blood flow capacity: Differences with interval sprint training versus aerobic endurance training. *Journal of Physiology and Pharmacology*, *59*, 71–88.

Lautenschlager, N. T., Cox, K., & Cyarto, E. V. (2012). The influence of exercise on brain aging and dementia. *Biochimica et Biophysica Acta*, *1822*, 474–481. http://doi.org/10.1016/j.bbadis.2011.07.010

Lavie, C. J., Arena, R., Swift, D. L., Johannsen, N. M., Sui, X., Lee, D., … Blair, S. N. (2015). Exercise and the Cardiovascular System Clinical Science and Cardiovascular Outcomes. *Circulation Research*, 207–220. http://doi.org/10.1161/CIRCRESAHA.117.305205

Law, M. R., Morris, J. K., & Wald, N. J. (2009). Use of blood pressure lowering drugs in the prevention of cardiovascular disease : meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *British Medical Journal*. http://doi.org/10.1136/bmj.b1665

Lear, S. A., Hu, W., Rangarajan, S., Gasevic, D., Leong, D., Iqbal, R., … Yusuf, S. (2017). The effect of physical activity on mortality and cardiovascular disease in

130 000 people from 17 high-income, middle-income, and low-income countries: The PURE study. *The Lancet*, *390*(10113), 2643–2654. http://doi.org/10.1016/S0140-6736(17)31634-3

Lenk, K., Uhlemann, M., Schuler, G., & Adams, V. (2011). Mechanism of Beneficial Effects of Physical Activity Role of endothelial progenitor cells in the beneficial effects of physical exercise on atherosclerosis and coronary artery disease. *Journal of Applied Physiology*, *111*, 321–328. http://doi.org/10.1152/japplphysiol.01464.2010.

Li, J., Loerbroks, A., & Angerer, P. (2013). Physical activity and risk of cardiovascular disease : what does the new epidemiological evidence show ? *Current Opinion in Cardiology*, *28*, 575–583. http://doi.org/10.1097/HCO.0b013e328364289c

Li, J., & Siegrist, J. (2012). Physical Activity and Risk of Cardiovascular Disease — A Meta-Analysis of Prospective Cohort Studies. *International Journal of Environmental Research and Public Health*, *9*, 391–407. http://doi.org/10.3390/ijerph9020391

Lobelo, F., Duperly, J., & Frank, E. (2008). Physical activity habits of physicians and medical students influence their counseling practices. *Centers for Disease Control and Prevention BJSM Online First*, 1–13. http://doi.org/10.1136/bjsm.2008.055426

Loke, Y., Singh, S., & Furberg, C. (2009). Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *Canadian Medical Association Journal*, *180*(1).

Maiorana, A., O'Driscoll, G., Taylor, R., & Green, D. (2003). Exercise and the nitric oxide vasodilator system. *Sports Medicine*, *33*, 1013–1035.

Mariotto, A. B., Yabroff, K. R., Shao, Y., Feuer, E. J., & Brown, M. L. (2011). Projections of the Cost of Cancer Care in the United States : 2010 – 2020. *Journal of the NAtional Cancer Institution*, *103*, 117–128. http://doi.org/10.1093/jnci/djq495

Martin, W., Dalsky, G., & Hurley, B. (1993). Effect of endurance training on plasma free fatty acid turnover and oxidation during exercise. *American Journal of Physiology*, *265*(708–14).

Matta, E., Cevada, T., & Monteiro-junior, S. (2013). Neuroscience of Exercise : From Neurobiology Mechanisms to Mental Health. *Neuropsychobiology*, 1–14. http://doi.org/10.1159/000350946

Mckenzie, D. C. (2012). Respiratory physiology : adaptations to high-level exercise. *British Journal of Sports Medicine*, 381–384. http://doi.org/10.1136/bjsports-2011-090824

McMurray, R., & Hackney, A. (2005). Interactions of Metabolic Hormones, Adipose Tissue and Exercise. *Sports Medicine*, *35*(5), 393–412.

Mctiernan, A. (2006). Relation of BMI and physical activity to sex hormones in postmenopausal women. *Obesity*, *14*, 1662–1677.

McTiernan, A. (2008). Mechanisms linking physical activity with cancer. *National Review Cancer*, *8*(January), 205–211. http://doi.org/10.1038/nrc2325

McTiernan, A., Tworoger, S., Ulrich, C., Yasui, Y., Irwin, M., Rajan, K., … Schwartz, R. (2004). Effect of Exercise on Serum Estrogens in Postmenopausal Women: A 12-Month Randomized Clinical Trial. *Cancer Research*, *64*, 2923–2928.

Meex, R., Schrauwen-Hinderling, V., Moonen-Kornips, E., Schaart, G., Mensink, M., Phielix, E., … MK., H. (2010). Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. *Diabetes*, *59*, 572–579.

Meredith, I. T., Jennings, G., & Esler, M. (1990). Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. *Journal of Hypertension*, *8*, 859–866.

Montori, V. M., & Fernandez-Balsells, M. (2009). Glycemic Control in Type 2 Diabetes : Time for an Evidence-Based About Face. *Annals of Internal Medicine*, 803–809.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., … Turner, M. B. (2016a). AHA Statistical Update Heart Disease and Stroke Statistics — 2016 Update A Report From the American Heart Association. *Circulation*, *133*, e38–e360. http://doi.org/10.1161/CIR.0000000000000350

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., … Turner, M. B. (2016b). Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*, *133*, e38–e360. http://doi.org/10.1161/CIR.0000000000000350

Naci, H., & Ioannidis, J. P. A. (2013). Comparative effectiveness of exercise and drug interventions on mortality outcomes : metaepidemiological study. *British Medical Journal*, *5577*(October), 1–14. http://doi.org/10.1136/bmj.f5577

National Center for Health Statistics. (2016). *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyatsville, MD.

Newcomer, S. C., Thijssen, D. H. J., & Green, D. J. (2011). Effects of exercise on endothelium and endothelium / smooth muscle cross talk : role of exercise-induced hemodynamics. *Journal of Applied Physiology*, *111*, 311–320. http://doi.org/10.1152/japplphysiol.00033.2011.

Nieman, D. (1994). Exercise, upper respiratory tract infection, and the immune system. *Medicine and Science in Sport and Exercise*, *26*, 128–139.

Nissen, S. E., & Wolski, K. (2007). Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *The New England Journal of Medicine*, *356*(24), 2457–2471.

Nissen, S. E., & Wolski, K. (2010). Rosiglitazone Revisited An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. *Archives of Internal Medicine*, *170*(14), 1191–1201. http://doi.org/10.1001/archinternmed.2010.207

On On Chan, A., Jim, M. H., Lam, K. F., Morris, J., Siu, D. C. W., Tong, T., … Lam, S. K. (2007). Prevalence of Colorectal Neoplasm Among Patients With Newly Diagnosed Coronary Artery Disease. *JAMA*, *298*(12).

Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., … Wilmore, J. H. (1995). Public Health and Prevention and the American College of Sports Medicine. *JAMA*, *273*(5), 402–407.

Paterson, D., Shephard, R., Cunningham, D., Jones, N., & Andrew, G. (1979). Effects of physical training on cardiovascular function following myocardial infarction. *Journal of Applied Physiology*, *47*(3), 482–489.

Patterson, S. L., Abel, T., Deuel, T. A. S., Martin, K. C., Rose, J. C., & Kandel, E. .

(1996). Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*, *16*, 1137–1145.

Patti, M., Butte, A., Crunkhorn, S., Cusi, K., Berria, R., Kashyap, S., … Mandarino, L. (2003). Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *PNAS*, *100*, 8466–8471.

Pedersen, B., & Hoffman-Goetz, L. (2000). Exercise and the immune system: regulation, integration and adaptation. *Physiology Review*, *80*, 1055–1081.

Pescatello, L. S., Miller, B., Danias, P., Werner, M., Hess, M., Baker, C., & De Souza, M. (1999). Dynamic exercise normalizes resting blood pressure in mildly hypertensive premenopausal women. *American Heart Journal*, *138*, 916–921.

Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, *98*(4), 1154–1162. http://doi.org/10.1152/japplphysiol.00164.2004.

Peterson, J. A. (2007). Get moving! Physical activity counseling in primary care. *Journal of the American Academy of Nurse Practitioners*, *19*(7), 349–357. http://doi.org/10.1111/j.1745-7599.2007.00239.x

Physical Activity Guidelines Advisory Committee. (2008). *Physical Activity Guidelines Advisory Committee Report, 2008*. Washinton D.C.

Powers, S. K., Dodd, S., Lawler, J., Landry, G., Kirtley, M., Mcknight, T., & Grinton, S. (1988). Incidence of exercise induced hypoxemia in elite endurance athletes at sea level Scott. *European Journal of Applied Physiology and Occupational Physiology*, 298–302.

Radak, Z., Hart, N., Sarga, L., Koltai, E., Atalay, M., & Ohno, H. (2010). Exercise Plays a Preventive Role Against Alzheimer ' s Disease. *Journal of Alzheimer's Disease*, *20*, 777–783. http://doi.org/10.3233/JAD-2010-091531

Rebar, A. L., Stanton, R., Geard, D., Short, C., & Duncan, M. J. (2015). A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychology Review*, *9*(3), 366–378. http://doi.org/10.1080/17437199.2015.1022901

Richards, J. C., Mckenzie, D. C., Warburton, D. E. R., Road, J. D., & Sheel, A. W. (2004). Prevalence of Exercise-Induced Arterial Hypoxemia in Healthy Women. *Medicine and S*, (12). http://doi.org/10.1249/01.MSS.0000139898.30804.60

Richter, E., & Hargreaves, M. (2013). Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiology Review*, *93*, 993–1017.

Risan, W. (1997). Mechanisms of angiogenesis. *Nature*, *386*, 671–674.

Rivera-brown, A. M., & Frontera, W. R. (2012). Principles of Exercise Physiology: Responses to Acute Exercise and Long-term Adaptations to Training. *The Journal of Injury Function and Rehabilitation*, *4*(11).

Robsahm, T. E., Aagnes, B., Hjartaker, A., Langseth, H., Bray, F. I., & Larsen, I. K. (2013). Body mass index, physical activity, and colorectal cancer by anatomical subsites : a systematic review and meta-analysis of cohort studies. *European Journal of Cancer Prevention*, 1–14. http://doi.org/10.1097/CEJ.0b013e328360f434

Rockl, K., Witczak, C., & Goodyear, L. (2008). Signaling mechanisms in skeletal muscle: acute responses and chronic adaptations to exercise. *IUBMB Life*, *60*, 145–53.

Rourk, Z., Abraham, I., Olson, T., & Snyder, E. (2018). *An Updated Assessment of The Clinical and Economic Burden of Physical Inactivity on the US Healthcare System and an Analysis for Potential Change*.

Rourk, Z., Olson, T., & Snyder, E. (2018). *Assessment of Providers' Knowledge and Understanding of the American College of Sports Medicine Exercise is Medicine® Initiative*.

Sale, D., MacDougall, J., & Jacobs, I. (1990). Interaction between concurrent strength and endurance training. *Journal of Applied Physiology*, *68*, 260–70.

Sallis, R. E., Matuszak, J. M., Baggish, A. L., Franklin, B. A., Chodzko-Zajko, W., Fletcher, B. J., … Williams, J. (2016). Call to action on making physical activity assessment and prescription a medical standard of care. *Current Sports Medicine Reports*, *15*(3), 207–214. http://doi.org/10.1249/JSR.0000000000000249

Sattelmair, J., Pertman, J., Ding, E., Kohl III, H., Haskell, W., & Lee, I. (2011). Dose-Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis. *Circulation*, *124*(7), 789–795. http://doi.org/10.1161/CIRCULATIONAHA.110.010710.Dose-Response

Schantz, P., Sjoberg, B., & Svedenhag, J. (1986). Malate-aspartate and alphaglycerophosphate shuttle enzyme levels in human skeletal muscle: methodological considerations and effect of endurance training. *Acta Physiol Scand*, *128*, 397–407.

Schuler, G., Adams, V., & Goto, Y. (2013). Role of exercise in the prevention of cardiovascular disease : results, mechanisms, and new perspectives. *European Heart Journal*, *34*, 1790–1799. http://doi.org/10.1093/eurheartj/eht111

Sedentary Behaviour Research Network. (2012). Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours." *Applied Physiology, Nutrition, and Metabolism*, *37*(3), 540–2. http://doi.org/10.1139/h2012-024

Seiler, C. (2003). THE HUMAN CORONARY COLLATERAL CIRCULATION. *Heart*, *89*, 1352–1357.

Shephard, R. (1992). Exercise physiology and performance of sport. *Sports Science Review*, *1*, 1–12.

Shulman, G., Rothman, D., Jue, T., Stein, P., DeFronzo, R., & Shulman, R. (1990). Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. *New England Journal of Medicine*, *322*(4), 223–228.

Silveira, H., Moraes, H., Oliveira, N., Coutinho, E. S. F. S., Laks, J., & Deslandes, A. (2013). Physical Exercise and Clinically Depressed Patients : A Systematic Review and Meta-Analysis. *Neuropsychobiology*, *67*, 61–68. http://doi.org/10.1159/000345160

Simoneau, J.-A., Lortie, G., & Boulay, M. (1985). Human skeletal muscle fibre alteration with high intensity intermittent training. *Journal of Applied Physiology*, *54*, 250–3.

Sofi, F., Capalbo, A., Cesari, F., Abbate, R., & Franco, G. (2008). Physical activity during leisure time and primary prevention of coronary heart disease : an updated meta-analysis of cohort studies. *European Journal of Cardiovascular Prevention and Rehabilitation*.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2010). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of Internal Medicine*, 107–117. http://doi.org/10.1111/j.1365-2796.2010.02281.x

Solomon, S. D., Wittes, J., Finn, P. V, Fowler, R., Viner, J., Bertagnolli, M. M., … Assessment, S. (2008). Cardiovascular Risk of Celecoxib in 6 Randomized Placebo-Controlled Trials: The Cross Trial Safety Analysis. *Circulation*, 2104–2113. http://doi.org/10.1161/CIRCULATIONAHA.108.764530

Spina, R., Chi, M., & Hopkins, M. (1996). Mitochondrial enzymes increase in muscle in response to 7-10 days of cycle exercise. *Journal of Applied Physiology*, *80*, 2250–4.

Stanford, K. I., & Goodyear, L. J. (2014). Exercise and type 2 diabetes : molecular mechanisms regulating glucose uptake in skeletal muscle Akt TBC1D1. *Advanced Physiology Education*, *2215*, 308–314. http://doi.org/10.1152/advan.00080.2014

Steiner, S., Niessner, A., Ziegler, S., Richter, B., Seidinger, D., Pleiner, J., … Kopp, C. (2005). Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease. *Atherosclerosis*, *181*, 305–310.

Stephens, J., & Pekala, P. (1991). Transcriptional repression of the GLUT4 and CIEBP genes in 3T3-L1 adipocytes by tumor necrosis factor-alpha. *Journal of Biological Chemistry*, *266*(21839–21845).

Stranahan, A. M., Lee, Æ. K., & Mattson, Æ. M. P. (2008). Central Mechanisms of HPA Axis Regulation by Voluntary Exercise. *Neuromol Med*, 118–127. http://doi.org/10.1007/s12017-008-8027-0

Strasser, B., & Pesta, D. (2013). Resistance Training for Diabetes Prevention and Therapy : Experimental Findings and Molecular Mechanisms. *Biomed Research International*.

Stuewe, S. R., Gwirtz, P. A., Agarwal, N., & Mallet, R. T. (2000). Exercise Training Enhances Glycolytic and Oxidative Enzymes in Canine Ventricular Myocardium. *Journal of Molecular and Cellular Cardiology*, *913*, 903–913. http://doi.org/10.1006/jmcc.2000.1131

Suhara, T., Magrane, J., Rosen, K., Christensen, R., Kim, H. ., Zheng, B., … Querfurth, H. (2003). Abeta42 generation is toxic to endothelial cells and inhibits eNOS function through an Akt/GSK-3beta signaling-dependent mechanism. *Neurobiology and Aging*, *24*, 437–451.

Suter, E., Hoppeler, H., & Claassen, H. (1995). Ultrastructural modification of human skeletalmuscle tissue with 6-month moderateintensity exercise training. *International Journal of Sports Medicine*, *16*, 160–6.

Swift, D. L., Johannsen, N. M., Lavie, C. J., Earnest, C. P., & Church, T. S. (2017). ScienceDirect The Role of Exercise and Physical Activity in Weight Loss and Maintenance. *Progress in Cardiovascular Diseases*, *56*(4), 441–447. http://doi.org/10.1016/j.pcad.2013.09.012

Swinburn, B., Walter, L., Arroll, B., Tilyard, M., & Russel, D. (1998). The Green

Prescription Study: A Randomized Controlled Trial of Written Exercise Advice Provided by General Practitioners. *American Journal of Public Health*, *88*(2), 1993–1996.

Thompson, P. D., Crouse, S. F., Goodpaster, B., Kelley, D., Moyna, N., & Pescatello, L. (2001). The acute versus the chronic response to exercise. *Medicina and Science in Sport and Exercise*, *33*(6), 438–445.

Tolppanen, A., Solomon, A., Kulmala, J., Ingemar, K., Ngandu, T., Rusanen, M., … Kivipelto, M. (2015). Leisure-time physical activity from mid-to late life, body mass index, and risk of dementia. *Alzheimer's and Dementia*, *11*(2015), 434–443. http://doi.org/10.1016/j.jalz.2014.01.008

Torre, J. (2002). Vascular basis of Alzheimer's pathogenesis. *Ann N Y Acad Sci*, *977*, 196–215.

Troiano, R. P., Berrigan, D., Dodd, K. W., Mâsse, L. C., Tilert, T., McDowell, M., … McDowell, M. (2008). Physical activity in the United States measured by accelerometer. *Medicine and Science in Sports and Exercise*, *40*(1), 181–188. http://doi.org/10.1249/mss.0b013e31815a51b3 [doi]

Tucker, J. M., Welk, G. J., & Beyler, N. K. (2011). Physical Activity in U.S. Adults Compliance with the Physical Activity Guidelines for Americans. *American Journal of Preventive Medicine*, *40*(4), 454–461. http://doi.org/10.1016/j.amepre.2010.12.016

Tworoger, S., Eliassen, A., & Kelesidis, T. (2007). Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metab*, *92*, 1510–1516.

Urbich, C., & Dimmeler, S. (2004). Endothelial progenitor cells. Characterization and role in vascular biology. *Circulation Research*, *95*, 343–353.

US Department of Health and Human Services. (2014). Physical Activity. Retrieved from https://www.healthypeople.gov/2020/topics-objectives/topic/physical-activity/objectives

Vahabzadeh, A., Delaffon, V., & Abbas, M. (2010). Cholinesterase inhibitors in Alzheimer's disease — an update. *GM2 Midlife and Beyond*, (October), 7–11.

Vaynman, S., & Gomez-Pinilla, F. (2006). Revenge of the"sit": how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. *Journal of Neuroscience Research, 84,* 699–715.

Vaynman, S., Ying, Z., & Gomez-pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, *20*(April), 2580–2590. http://doi.org/10.1111/j.1460-9568.2004.03720.x

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2003). Interplay between BDNF and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. *Neuroscience*, *122*, 647–657.

Verkasalo, P. K., Thomas, H. V., Appleby, P. N., Davey, G. K., & Key, T. J. (2001). Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control*, *12*, 47–59.

Vogel, V. G., Costantino, J. P., Wickerham, D. L., Cronin, W. M., Cecchini, R. S., Atkins, J. N., … Wolmark, N. (2010). Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial : Preventing Breast Cancer. *Cancer Prevention Research*, *3*(June), 696–707. http://doi.org/10.1158/1940-6207.CAPR-10-0076

Vuori, I. M., Lavie, C. J., & Blair, S. N. (2013). Physical activity promotion in the health care system. *Mayo Clinic Proceedings*, *88*(12), 1446–1461. http://doi.org/10.1016/j.mayocp.2013.08.020

Wadgave, U., & Khairnar, M. R. (2016). Parametric tests for Likert scale: For and against. *Asian Journal of Psychiatry*, *24*(March 2018), 67–68. http://doi.org/10.1016/j.ajp.2016.08.016

Wagenmakers, A., Beckers, E., Brouns, F., Kuipers, H., Soeters, P., Van der Vusse, G., & Saris, W. (1991). Carbohydrate supplementation, glycogen depletion, and amino acid metabolism during exercise. *American Journal of Physiology*, *260*, 883–890.

Wang, G., Pratt, M., Macera, C. A., Zheng, Z.-J., & Heath, G. (2004). Physical activity, cardiovascular disease, and medical expenditures in U.S. adults. *Annals of Behavioral Medicine*, *28*(2), 88–94.

Wee, C. C., McCarthy, E. P., Davis, R. B., & Phillips, R. S. (1999). Physician Counseling About Exercise. *Jama*, *282*(16), 1583. http://doi.org/10.1001/jama.282.16.1583

Wegner, M., Helmich, I., Machado, S., Nardi, A. E., & Arias-carrión, O. (2014). Effects of Exercise on Anxiety and Depression Disorders : Review of Meta- Analyses and Neurobiological Mechanisms. *CNS & Neurological Disorders - Drug Targets*, 1002–1014.

Wimo, A., Winblad, B., Jonsson, L., & Jo, L. (2010). The worldwide societal costs of dementia : Estimates for 2009. *Alzheimer's & Dementia*, *6*, 98–103. http://doi.org/10.1016/j.jalz.2010.01.010

Wolin, K. Y., Yan, Y., Colditz, G. A., & Lee, I. (2009). Physical activity and colon cancer prevention : a meta-analysis. *British Journal of Cancer*, *100*, 611–616. http://doi.org/10.1038/sj.bjc.6604917

Wu, Y., Zhang, D., & Kang, S. (2013). Physical activity and risk of breast cancer : a meta-analysis of prospective studies. *Breast Cancer Research and Treatment*, *137*(38), 869–882. http://doi.org/10.1007/s10549-012-2396-7

Xu, X., Bishop, E., Kennedy, S., Simpson, S., & Pechacek, T. (2015). Annual Healthcare Spending Attributable to Cigarette Smoking: An Update. *American Journal of Preventative Medicine*, *48*(3), 95–121. http://doi.org/10.1007/128

Yuan, T., Paes, F., Arias-carrión, O., Barbosa, N., Rocha, F., Souza, A., … Machado, S. (2015). Neural Mechanisms of Exercise : Anti-Depression , Neurogenesis , and Serotonin Signaling. *CNS & Neurological Disorders - Drug Targets*, 1307–1311.

Zhao, Y., & Zhao, B. (2013). Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid Med Cell Longev*.

Zouhal, H., Jacob, C., Delamarche, P., & Gratas-Delamarche, A. (2008). Catecholamines and the Effects of Exercise, Training and Gender. *Sports Medicine*, *38*(5), 401–423.

Tables

Table 1. Retrieved Data and Sources

Disease Type	Prevalence	Cause of Death Rank	DMC (Billions of USD)	Relative Risk (95% CI)
Cardiovascular Disease	85,600,000[3]	1[7]	$187.68[3]	0.86 (0.77-0.96)[11]
Type II Diabetes Mellitus	27,010,000[3]	7[7]	$183.98[3]	0.65 (0.59–0.71)[12]
Depression	16,100,000[6]	10 (Suicide)[7]	$103.39[8]	0.67 (0.49-0.91)[13]
Alzheimer's Disease	5,300,000[4]	6[7]	$77.71[9]	0.55 (0.36–0.84)[14]
Breast Cancer	3,461,000[5]	2 (All Cancer)[7]	$18.38[5]	0.88 (0.85–0.91)[15]
Colon Cancer	1,216,000[5]	2 (All Cancer)[7]	$15.75[5]	0.88 (0.86–0.91)[16]
Stroke	6,600,000[3]	5[7]	$18.35[3]	0.843 (0.779-0.918)[17]
Total	145,287,000		605.24	

Table 2. Relative Risk of Disease Given Either Physical Activity or Pharmacological Intervention

Condition	Study Type	# of Studies	N	Intervention Type	Authors	Year	Relative Risk (95% C.I.)	Intervention Group	Comparison Group
Cardiovascular Disease	Meta-Analysis	26	513,472	Physical Activity	Sofi, Capalbo, Cesari, Abbate and Gensini[20]	2008	0.73 (0.66–0.80)	High PA	Low PA
							0.88 (0.83–0.93)	Moderate PA	Low PA
	Meta-Analysis	33	NA	Physical Activity	Sattelmair, Pertman, Ding, Kohl III, Haskell, Lee[11]	2011	0.80 (0.74–0.88)	300 min/week of moderate-intensity PA	No PA
							0.86 (0.77–0.96)	150 min/week of moderate-intensity PA	No PA
	Meta-Analysis	21	>650,000	Physical Activity	Li and Siegrist[21]	2012	0.79 (0.73-0.85)	High PA (Men)	Low PA (Men)
							0.85 (0.77-0.93)	Moderate PA (Men)	Low PA (Men)
							0.71 (0.65-0.77)	High PA (Women)	Low PA (Women)
							0.78 (0.72-0.85)	Moderate PA (Women)	Low PA (Women)
	Meta-Analysis	23	790,000	Physical Activity	Li, Loerbroks and Angerer[22]	2013	0.79 (0.73-0.85)	High PA	Low PA
							0.71 (0.65-0.77)	Moderate PA	Low PA
	Meta-Analysis	147	464,000	Pharmacological	Law, Morris, & Wald[23]	2009	0.85 (0.81-0.89)	All Classes of Blood Pressure Medication	Placebo
Stroke	Meta-Analysis	13	255,873	Physical Activity	Diep, Kwagyan, Kurantsin-Mills, Weir, Jayam,Trouth[24]	2010	0.81 (0.77-0.84)	High PA	Low PA
							0.89 (0.86-0.93)	Moderate PA	Low PA
	Meta-Analysis	21	>650,000	Physical Activity	Li and Siegrist[21]	2012	0.71 (0.60-0.84)	High PA (Men)	Low PA (Men)
							0.89 (0.82–0.97)	Moderate PA(Men)	Low PA (Men)
							0.73 (0.68-0.78)	High PA (Women)	Low PA (Women)
							0.83 (0.67–1.03)	Moderate PA (Women)	Low PA (Women)
	Meta-Analysis	23	790,000	Physical Activity	Li, Loerbroks and Angerer[22]	2013	0.72 (0.58-0.90)	High PA	Low PA
							0.79 (0.72-0.88)	Moderate PA	Low PA
	Meta-Analysis	26	1,573,231	Physical Activity	Kyu, Bachman, Alexander, Mumford, Afshin, Estep, Veerman, Delwiche, Iannarone, Moyer, Cercy, Vos, Murray, Forouzanfar[17]	2016	0.736 (0.659-0.811)	8,000+ MET min/wk	<600 MET min/wk
							0.810 (0.690-0.937)	4000-7999 MET min/wk	<600 MET min/wk
							0.843 (0.779- 0.918)	600-3999 MET min/wk	<600 MET min/wk
	Meta-Analysis	147	464,000	Pharmacological	Law, Morris, & Wald[23]	2009	0.73 (0.66-0.80)	All Classes of Blood Pressure Medication	Placebo
Type II Diabetes Mellitus	Systematic Review	81	>1,800,000	Physical Activity	Aune, Norat, Leitzmann, Tonstad, and Vatten[12]	2015	0.65 (0.59-0.71)	High Total PA	Low Total PA
							0.74 (0.70-0.79)	High Leisure Time PA	Low Leisure Time PA
							0.61 (0.51-0.74)	High Vigorous PA	Low Vigorous PA
							0.68 (0.52-0.90)	High Moderate PA	Low Moderate PA
							0.66 (0.47-0.94)	High Low Intensity PA	Low Low Intensity PA
							0.85 (0.79-0.91)	High Walking	Low Walking
							0.72 (0.57-0.91)	High Resistance Exercise	Low Resistance Exercise
							0.85 (0.79-0.92)	High Occupational PA	Low Occupational PA
							0.45 (0.29-0.70)	High Cardiorespiratory Fitness	Low Cardiorespiratory Fitness
	Systematic Review	10	301,221	Physical Activity	Jeon, Hu, Lokken and van Dam[25]	2007	0.69 (0.58-0.83)	Regular Participation in Moderate PA	Sedentary
							0.70 (0.58-0.84)	Regular Walking	No Walking
	Consensus Workshop	11	15,772	Lifestyle or Pharmacological	Alberti, Zimmet and Shaw[26]	2007	0.37 (NA)	Lifestyle	Placebo
							0.58 (NA)	Lifestyle	Placebo
							0.42 (NA)	Lifestyle	Placebo
							0.42 (NA)	Lifestyle	Placebo
							0.37 (NA)	Lifestyle	Placebo
							0.72 (NA)	Lifestyle	Placebo
							0.69 (NA)	Metformin	Placebo
							0.74 (NA)	Metformin	Placebo
							0.45 (NA)	Troglitazone	Placebo
							0.25 (NA)	Troglitazone	Placebo
							0.75 (NA)	Acarbose	Placebo
							0.63 (NA)	Orlistat	Placebo
							0.40 (NA)	Rosiglitazone	Placebo

	Metaepidemiological Study	305	339,274	Physical Activity vs. Pharmacological	Naci and Loannidis[27]	2013	0.22 (0.02-1.18)	PA	AGIs
							2.67 (0.41-36.39)	PA	Biguanides
							0.73 (0.14-1.96)	PA	ACE Inhibitors
							0.69 (0.10-2.52)	PA	Glinides
Depression	Systematic Review and Meta-Analysis	10	758	Physical Activity	Silveira, Moraes, Oliveira, Coutinho, Laks, and Deslandes[13]	2013	1.49 (1.10-2.03)	Control	PA
							1.14 (0.97-1.35)	Control	PA
	Review of Meta-Analyses	833	48,207	Physical Activity	Wegner, Helmich, Machado, Nardi, Arias-Carrion and Budde[28]	2014	0.56 (0.31) Effect Size	The Effect of Physical Activity on Depression	
Alzheimer's Disease	Sysematic Review and Meta-Analysis	37	NA	Physical Activity	Blondell, Hammersley-Mather and Veerman[29]	2014	0.86 (0.76-0.97)[a]	High PA	Low PA
							0.65 (0.55-0.76)[b]	High PA	Low PA
	Systematic Review	16	163,797	Physical Activity	Hamer and Chida[14]	2008	0.72 (0.60-0.86)[a]	High PA	Low PA
							0.55 (0.36-0.84)	High PA	Low PA
	Meta-Analysis	3	3,574	Pharmacological	Diniz, Pinto Jr., Gonzaga, Guimaraes, Gattaz and Forlenza[31]	2009	0.75 (0.65-0.87)	Cholinesterase Inhibitors	Placebo
Breast Cancer	Meta-Analysis	31	63,786	Physical Activity	Wu, Zhang and Kang[15]	2013	0.88 (0.85-0.91)	High PA Overall	Low PA Overall
							0.90 (0.83-0.97)	High Occupational PA	Low Occupational PA
							0.87 (0.84-0.91)	High Non-Occupational PA	Low Non-Occupational PA
							0.89 (0.85-0.92)	High Recreational PA	Low Recreational PA
							0.89 (0.83-0.95)	High Household PA	Low Household PA
							0.88 (0.81-0.96)	High Walking	Low Walking
							0.97 (0.94-0.99)	High Moderate PA	Low Moderate PA
							0.86 (0.82-0.89)	High Vigorous PA	Low Vigorous PA
	Benefit/Risk Assesment	2	657	Pharmacological	Freedman, Yu, Gail, Constantino, Graubard, Vogel, Anderson and McCaskill-Stevens[32]	2011	0.59 (0.43-0.82)	Raloxifene[c]	Placebo
							0.51 (0.39-0.66)	Tamoxifen[c]	Placebo
Colon Cancer	Meta-Analysis	30	3,970,339	Physical Activity	Robsahm, Aagnes, Hjartaker, Langseth, Bray and Larsen[33]	2013	0.76 (0.70-0.83)[d]	High PA	Low PA
							0.77 (0.71-0.83)[e]	High PA	Low PA
	Meta-Analysis	21	11,093	Physical Activity	Johnson, Wei, Ensor, Smolenski, Amos, Levin and Berry[16]	2013	0.88 (0.86-0.91)[f]	High PA	Low PA
	Meta-Analysis	52	NA	Physical Activity	Wolin, Yan and Lee[35]	2009	0.76 (0.72-0.81)	High PA Overall	Low PA Overall
							0.76 (0.71-0.82)	High PA Men	Low PA Men
							0.79 (0.71-0.88)	High PA Women	Low PA Women
	Meta-Analysis	4	2,967	Pharmacological	Cole, Logan, Halabi, Benamouzig, Sandler, Grainge, Chaussade and Baron[36]	2009	0.83 (0.72-0.96)[f]	Aspirin	Placebo

[a]Relative risk for dementia

[b]Relative risk for cognitive decline

[c]Associated with toxic side effects, only used in patients already suffering from breast cancer

[d]Relative risk for cancer of the proximal colon

[e]Relative risk for cancer of the distal colon

[f]Relative risk for colorectal cancer

Table 3. Population Attributable Risk, Total Cases and Total DMC Attributable to Physical Inactivity

	Calculation based on NHIS Survey Data (P_{rf}= .565)			Calculation based on NHANES Accelerometry Data (P_{rf}= .904)		
Disease Type	PAR (95% CI)	Total Cases Attributable to Physical Inactivity	Total DMC Attributable to Physical Inactivity (Billions of USD)	PAR (95% CI)	Total Cases Attributable to Physical Inactivity	Total DMC Attributable to Physical Inactivity (Billions of USD)
Cardiovascular Disease	12.64% (3.49-20.78%)	10,819,840	$23.72	8.29% (2.21-14.08%)	7,096,240	$15.56
Type II Diabetes Mellitus	32.39% (27.04-38.41%)	8,748,539	$59.59	23.04% (18.80-28.05%)	6,223,104	$42.39
Depression	30.70% (8.29-48.22%)	4,942,700	$31.74	21.68% (5.35-36.79%)	3,490,480	$22.41
Alzheimer's Disease	42.57% (14.66-61.67%)	2,256,210	$33.08	31.66% (9.69-50.14%)	1,677,980	$24.60
Breast Cancer	11.23% (8.29-13.99%)	388,670	$2.06	7.33% (5.35-9.23%)	253,691	$1.35
Colon Cancer	11.23% (8.29-13.99%)	136,557	$1.77	7.33% (5.35-9.23%)	89,133	$1.15
Stroke	14.39% (7.45-20.43%)	949,740	$2.64	9.50% (4.78-13.83%)	627,000	$1.74
Total		28,242,256	$154.61		19,457,628	$109.21

Table 4. A Summary of the Potential Cases Prevented and Direct Medical Cost Saving for Each Analysis

Disease Type	Potential Clinical Cases Prevented			Potential Direct Medical Cost Savings (Billions of USD)		
	SurveyData	Accel10%	Accel4.4	SurveyData	Accel10%	Accel4.4
Cardiovascular Disease	510,138	100,487	462,794	$1,118.49	$220.32	$1,014.69
Type II Diabetes Mellitus	379,838	63,032	292,515	$2,393.24	$397.15	$1,843.04
Depression	216,566	36,492	169,240	$1,390.73	$234.34	$1,086.82
Alzheimer's Disease	91,563	13,823	64,402	$1,342.51	$202.67	$944.28
Breast Cancer	18,414	3,670	16,891	$97.79	$19.49	$89.70
Colon Cancer	6,470	1,289	5,935	$83.80	$16.70	$76.87
Stroke	44,560	8,650	39,863	$123.89	$24.05	$110.83
Total	1,267,548	227,443	1,051,640	$6,550.45	$1,114.72	$5,166.22

Table 5. Descriptive Statistics

	Overall N = 104	Doctors N = 85	Non-Doctors N = 19	MN N = 59	Non-MN N = 45
Specialty					
Family Practitioner	48	48	0	33	15
Pediatrician	23	23	0	15	8
Geriatrician	0	0	0	0	0
Internist	3	3	0	2	1
Obstetrician/Gynecologist	6	6	0	0	6
Nurse Practitioner	14	0	14	4	10
Physician's Assistant	2	0	2	1	1
Other (Doctor)	5	5	0	3	2
Other (Non-Doctor)	3	0	3	1	2
Medical Doctor (MD) or Doctor of Osteopathy (DO)					
MD	74	74	NA	48	26
DO	5	5	NA	2	3
DNA	6	6	NA	3	3
Percentage of Primary Care Patients Seen in Practice					
0-25%	15	10	5	4	11
26-50%	4	1	3	0	4
51-75%	3	3	0	1	2
76-100%	82	71	11	54	28
Years in Practice					
0-5 years	9	6	3	6	3
6-10 years	15	12	3	10	5
11-15 years	16	12	4	12	4
>15 years	64	55	9	31	33
Type of Practice					
Solo Practice	8	7	1	0	8
Group Practice	69	58	11	48	21
Hospital	7	4	3	3	4
Academics	2	2	0	0	2
VA/ Government	5	5	0	1	4
HMO	4	4	0	3	1
Other	9	5	4	4	5
Sex					
Male	38	38	0	26	12
Female	66	47	19	33	33
Age					
Average Age	52.27	51.64	54.79	49.70	55.14
Youngest	32	35	32	32	35
Oldest	78	78	68	76	78

Figures

Figure 1. Questions and Potential Answers

	Questions	Potential Responses	
Q48	Primary care practitioners should be assessing patient physical activity levels during all office visits, it is within their scope of	1	Strongly agree
Q49	Primary care practitioners should be determining patient exercise ability during all office visits, it is within their scope of practice.	2	Agree
Q50	Primary care practitioners should be utilizing behavioral counseling strategies directed at increasing physical activity during all office visits, it is within their scope of practice.	3	Somewhat agree
Q51	Primary care practitioners should be providing written prescriptions for physical activity during all office visits, it is within their scope of	4	Neither agree nor disagree
Q52	Primary care practitioners should be referring patients to exercise professionals when they deem it necessary, it is within their scope	5	Somewhat disagree
Q53	Primary care practitioners should execute all 5 steps of the EIM process at every office visit, it is within their scope of practice.	6	Disagree
		7	Strongly disagree

Figure 2. Primary Care Practitioner Attitude Towards EIM®: Overall

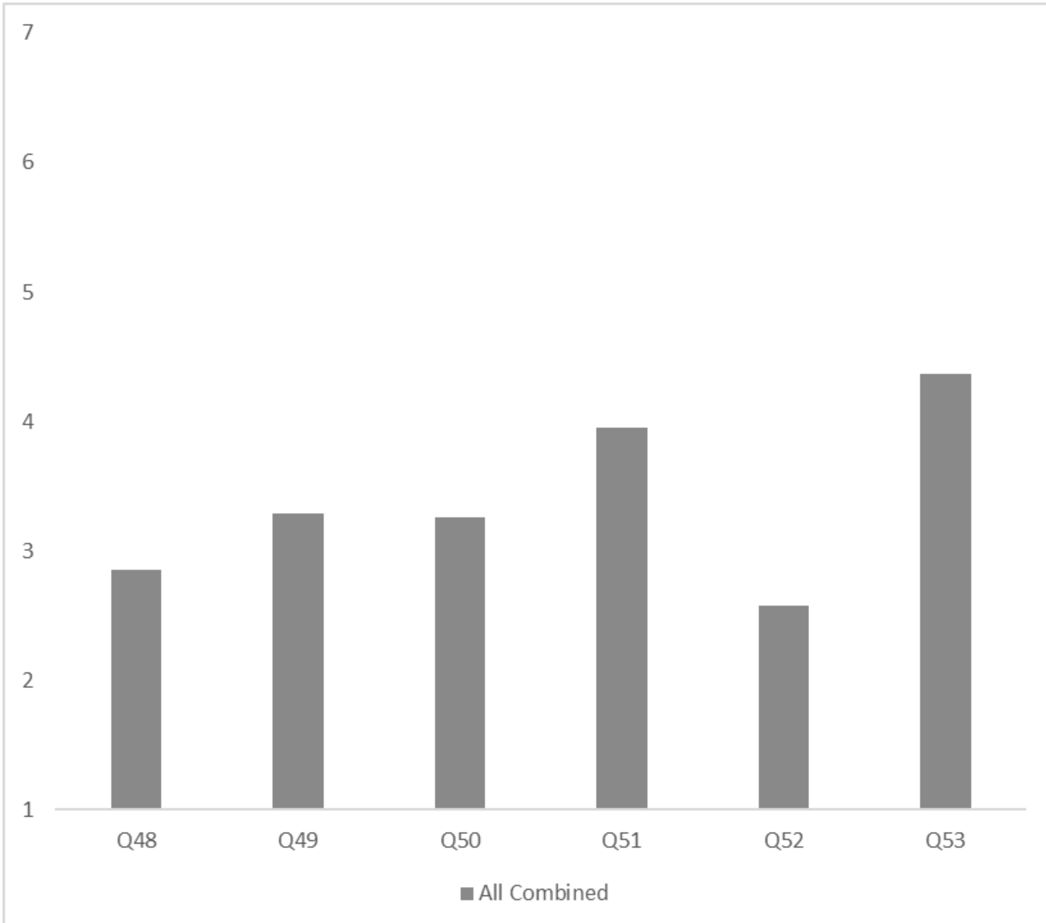

Figure 3. Primary Care Practitioner Familiarity with EIM®: Before taking part in this survey, which of the following best describes your knowledge of the EIM® initiative?

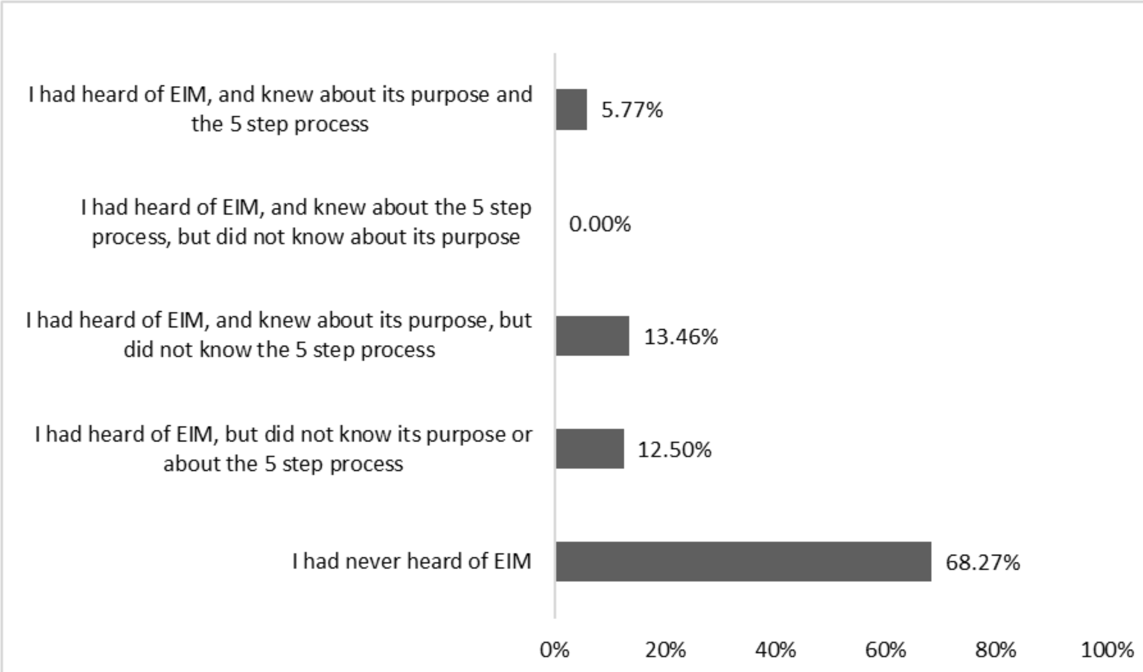

Figure 4. Primary Care Practitioner Implementation of the EIM®: During routine office visits, with what percentage of patients do you…

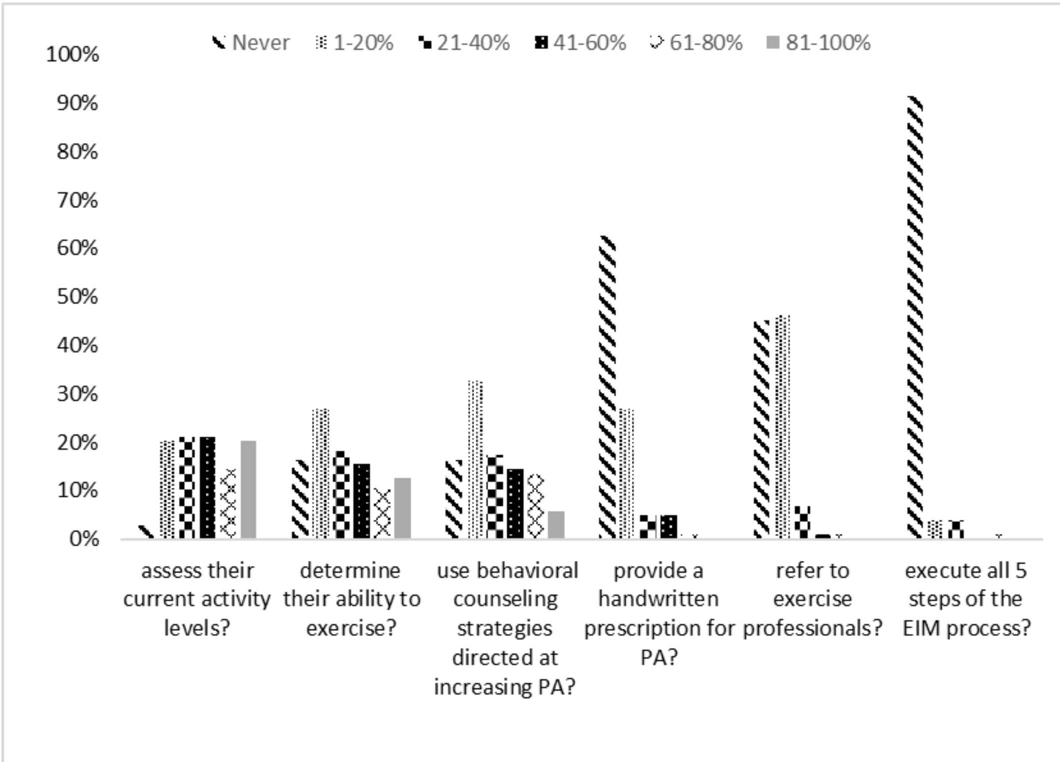

Figure 5. Primary Care Practitioner Implementation of the EIM®: When you do assess patient activity levels, do you use the Physical Activity Vital Screen (PAVS)?

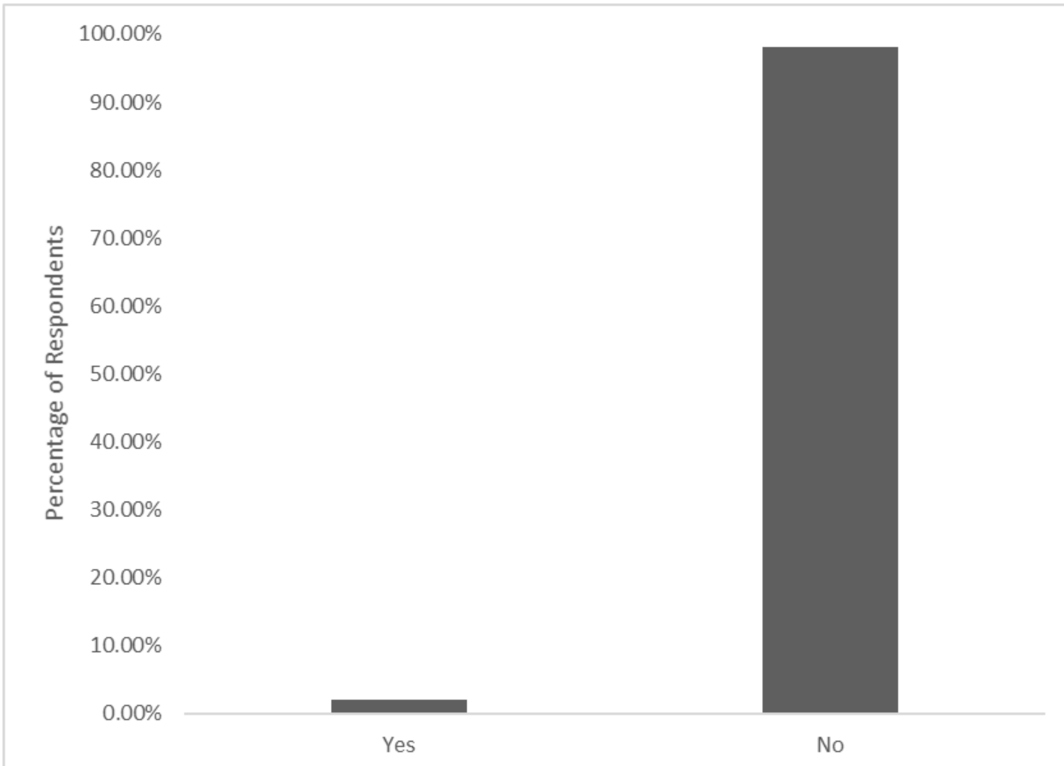

Figure 6. Primary Care Practitioner Implementation of the EIM®: When you do determine your patient's ability to exercise, do you use the Physical Activity Readiness Questionnaire (PAR-Q)?

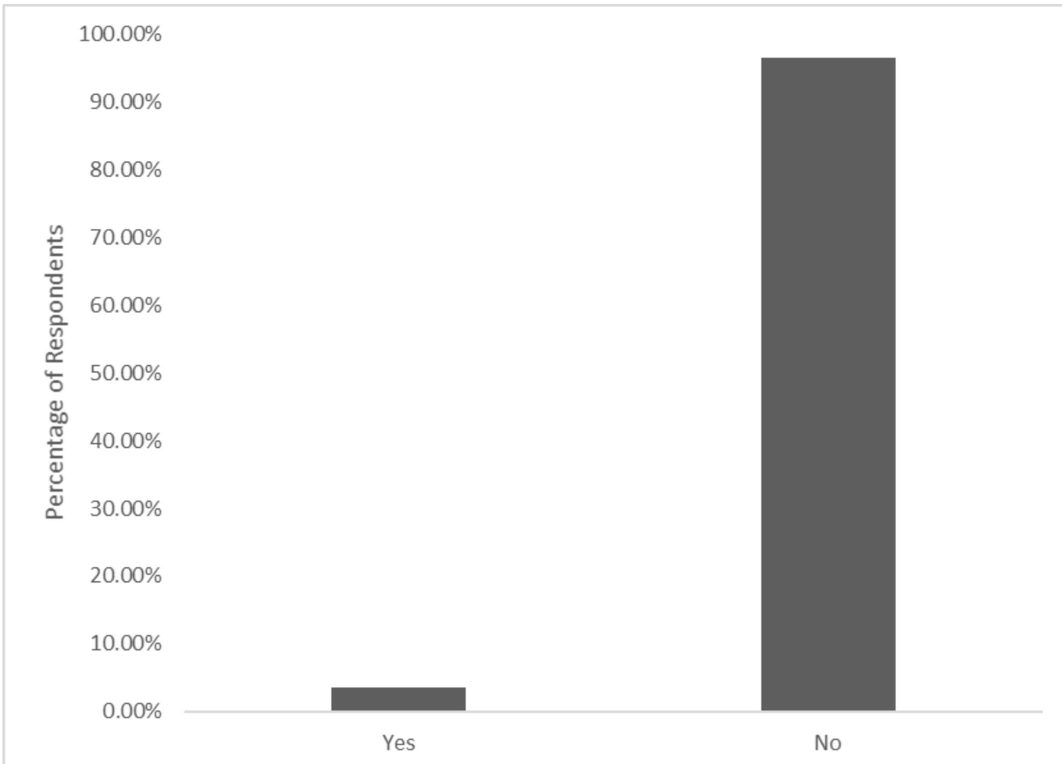

Figure 7. Primary Care Practitioner Implementation of the EIM®: When you do use behavioral counseling strategies, do you use The Exercise Stages of Change Model?

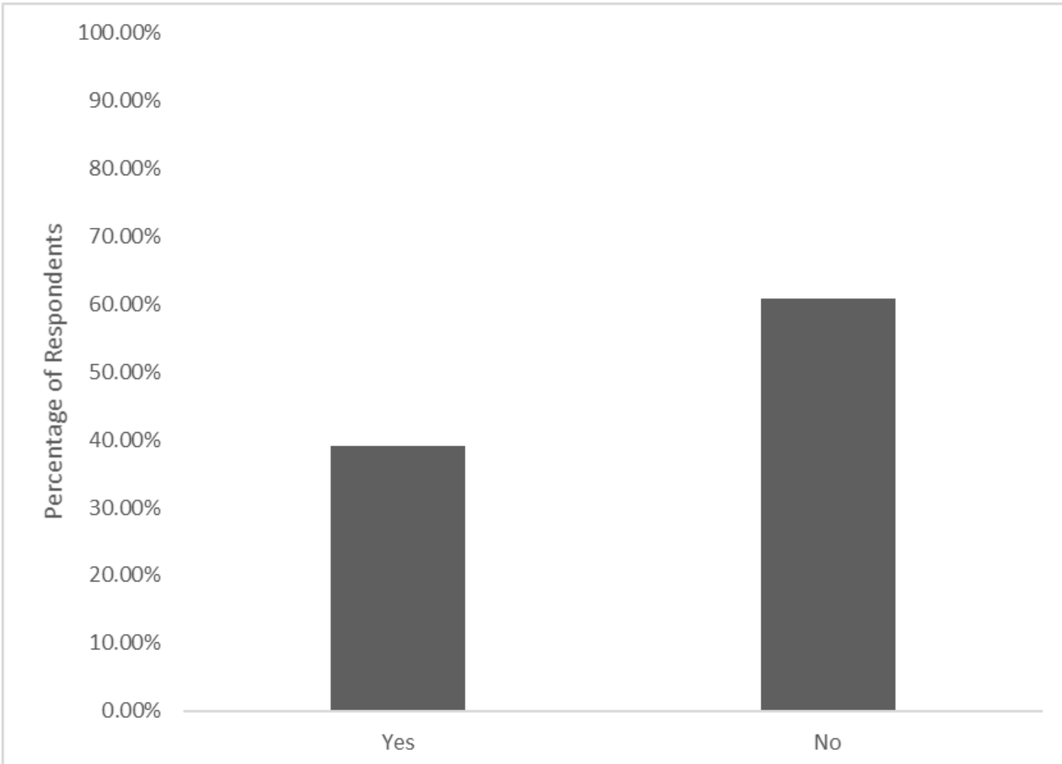

Figure 8. If all five steps of the EIM® process were carried out by all primary care practitioners during all office visits, how would the physical activity level of the patient population be affected?

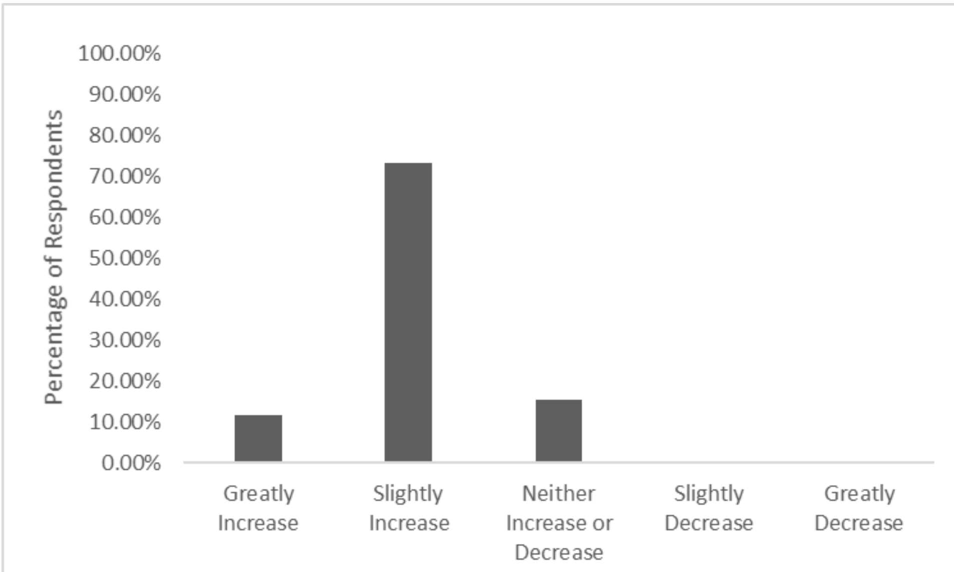

Figure 9. Primary Care Practitioners Attitude Towards EIM®: Doctor vs. Non-Doctor

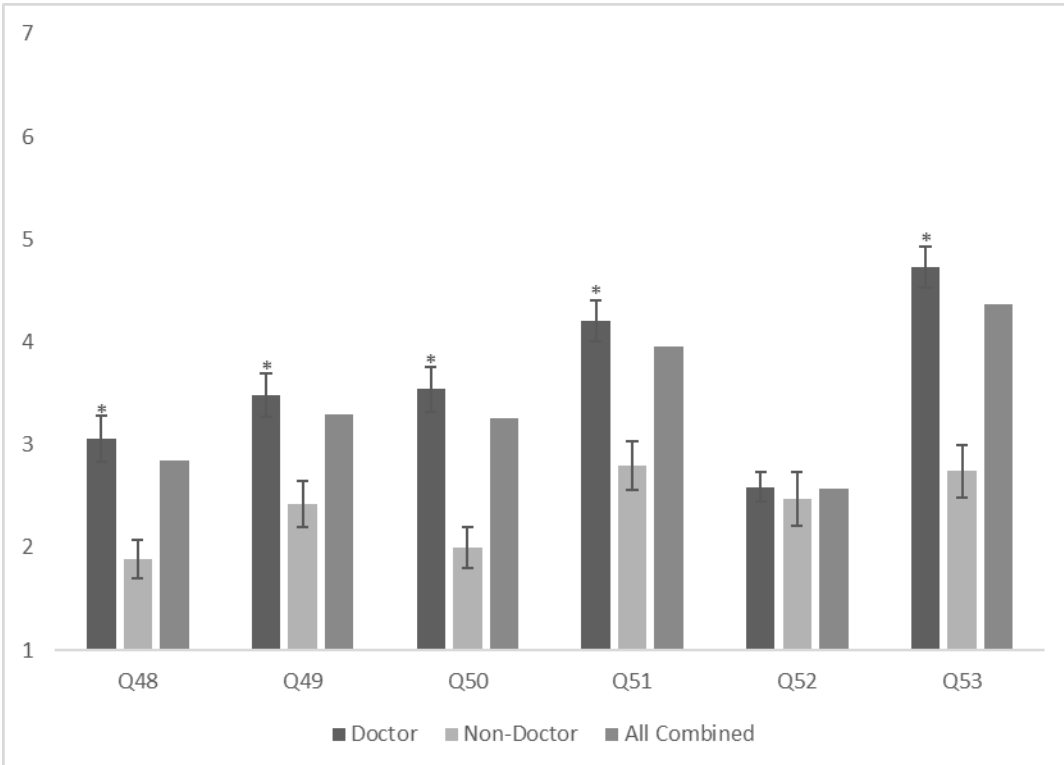

Figure 10. Primary Care Practitioners Attitude Towards EIM®: MN vs. Non-MN

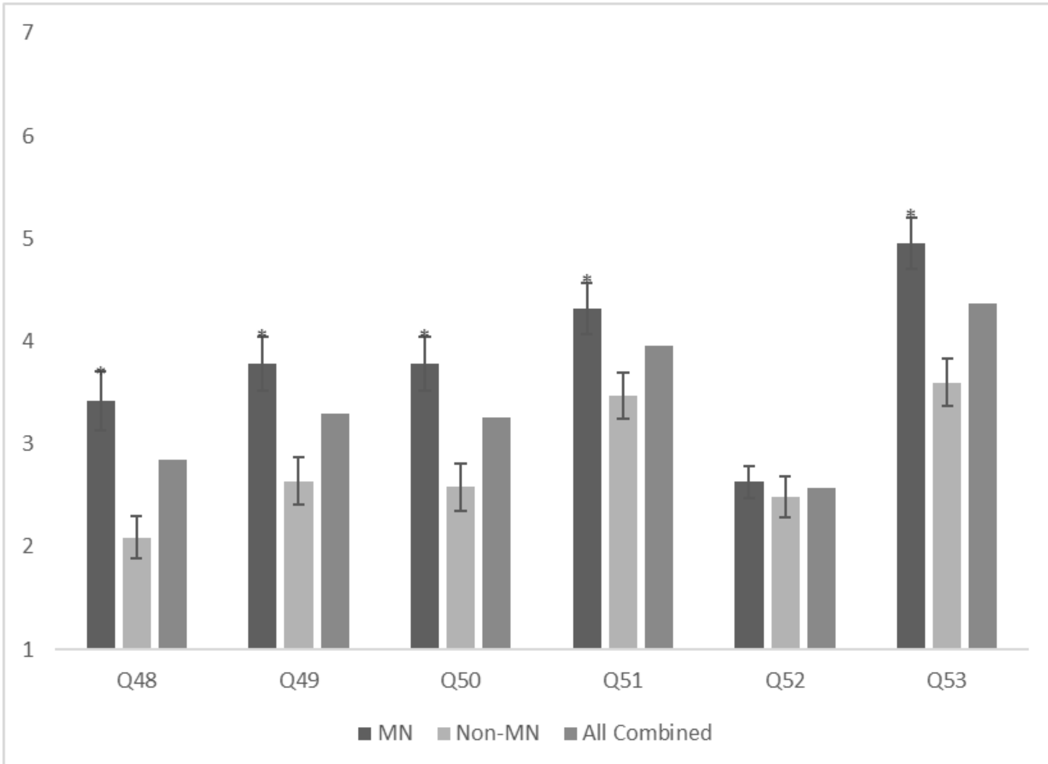

Figure 11. Comparison of the Proposed Amended EIM® Strategy and the Current EIM® Strategy

Amended EIM® Strategy	Current EIM® Strategy
Steps for Primary Care Practitioners	Steps for Primary Care Practitioners
1) PAVS and PAR-Q required in Electronic Medical Record System	1) Assess patient physical activity levels, using the Physical Activity Vital Sign (PAVS)
2) Primary care practitioners refer patients to exercise professionals when deemed necessary*	2) Assess patient physical activity ability, using the Physical Activity Readiness Questionnaire (PAR-Q)
	3) Counsel patients to increase physical activity, utilizing the Exercise Stages of Change model
Steps for ACSM and EIM® Planners	4) Prescribe physical activity to patients using handwritten prescriptions
1) Create a referral network of exercise professionals for primary care practitioners	5) Provide patients with referrals to exercise professionals when deemed necessary
2) Create awareness of the Amended EIM® strategy	

*Necessary refers to any patient that does not meet the current weekly physical activity recommendations or is symptomatic of disease related to sedentary lifestlye

Appendix

Section 1: Demographics

Q16 What is your specialty?

1. Family Practitioner
2. Pediatrician
3. Geriatrician
4. Internist
5. Obstetrician/Gynecologist
6. Nurse Practitioner
7. Physician's Assistant
8. Other (Please Describe) ________________

Q36 Are you a Medical Doctor (MD), or Doctor of Osteopathy (DO)?

1. Medical Doctor (MD)
2. Doctor of Osteopathy (DO)

Q17 Please indicate the percentage of primary care patients in your practice?

1. 0-25%
2. 26-50%
3. 51-75%
4. 76-100%

Q18 How long have you been in practice?

1. 0-5 years
2. 6-10 years
3. 11-15 years
4. >15 years

Q19 Which of the following best describes your practice, or the practice that you are a part of?

1. Solo Practice
2. Group Practice
3. Hospital
4. Academics
5. VA/ Government
6. HMO
7. Other (Please Describe) ____________________________

Q20 Are you male or female?

1. Male
2. Female

Q21 What is your date of birth? (mm/dd/yyyy) ________________________________

Q33 What state do you practice in? State Initials _____________________

Section 2: Current Awareness

Q34 Exercise is Medicine
The purpose of the Exercise is Medicine (EIM) initiative is to make the scientifically proven benefits of physical activity the standard in the U.S. healthcare system. The vision of EIM is to have healthcare providers assess every patient's level of physical activity at every clinic visit, determine if the patient is meeting the U.S. National Physical Activity Guidelines and provide patients with brief counseling to help him/her meet the guidelines and/or refer the patient to either healthcare or community-based resources for further physical activity (PA) counseling.

The 5 Step EIM Process The EIM model relies upon the implementation of a 5 step process, by primary care practitioners. This process is intended to be executed at every office visit and takes approximately 3-5 minutes. The steps are as follows.

1. Assess the patient's current activity levels using the Physical Activity Vital Sign (PAVS)
2. Determine the patient's ability to exercise using the Physical Activity Readiness Questionnaire (PAR-Q)
3.Counsel the patient using behavioral counseling strategies and The Exercise Stages of Change questionnaire (ESC-Q)
4. Provide a handwritten prescription for physical activity
5. Provide the patient with a referral to an exercise professional, when necessary

Before taking part in this survey, which of the following options best describes your knowledge of the EIM initiative?

1. I had never heard of EIM
2. I had heard of EIM, but did not know its purpose or about the 5 step process
3. I had heard of EIM, and knew about its purpose, but did not know the 5 step process
4. I had heard of EIM, and knew about the 5 step process, but did not know about its purpose
5. I had heard of EIM, and knew about its purpose and the 5 step process

Section 3: Current Clinical Use

Q35 During routine office visits, in what percentage of patients do you assess their current activity levels?

1. I never assess patient activity levels
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Q38 When you do assess patient activity levels, do you use the Physical Activity Vital Screen (PAVS)?

1. No
2. Yes

Q39 What type of screening tool or method do you use to assess patient activity levels? Please describe below.

____

Q36 During routine office visits, in what percentage of patients do you determine their ability to exercise?

1. I never determine a patient's ability to exercise
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Q40 When you do determine your patient’s ability to exercise do you use the Physical Activity Readiness Questionnaire (PAR-Q)?

1. No
2. Yes

Q41 What type of screening tool or method do you use to determine a patient's ability to exercise? Please describe below.

____

Q42 During routine office visits, with what percentage of patients do you use behavioral counseling strategies directed at increasing physical activity levels?

1. I never use behavioral counseling strategies directed at increasing physical activity levels
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Q43 When you do use behavioral counseling strategies do you use The Exercise Stages of Change (i.e. Pre-contemplation, Contemplation, Preparation, Action, Maintenance)?

1. No
2. Yes

Q44 What type of behavioral counseling strategy do you use directed at increasing the physical activity levels of your patients? Please describe below.

____

Q45 During routine office visits, with what percentage of patients do you provide a handwritten prescription for physical activity or exercise?

1. I never provide patients with handwritten prescriptions for exercise
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Q46 During routine office visits, what percentage of patients do you refer to exercise professionals?

1. I never refer patients to exercise professionals
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Q47 The 5 Step EIM Process

The EIM model relies upon the implementation of a 5 step process, by primary care practitioners. This process is intended to be executed at every office visit and takes approximately 3-5 minutes. The steps are as follows.

1. Assess the patient's current activity levels using the Physical Activity Vital Sign (PAVS)

2. Determine the patient's ability to exercise using the Physical Activity Readiness Questionnaire (PAR-Q)

3.Counsel the patient using behavioral counseling strategies and The Exercise Stages of Change questionnaire (ESC-Q)

4. Provide a handwritten prescription for physical activity

5. Provide the patient with a referral to an exercise professional, when necessary

During routine office visits, what percentage of patients do you execute all 5 steps of the EIM process with?

1. I never execute all 5 steps of the EIM process with a patient
2. 1-20%
3. 21-40%
4. 41-60%
5. 61-80%
6. 81-100%

Section 4: Scope of Practice

Q48 Primary care practitioners should be assessing patient physical activity levels during all office visits, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q49 Primary care practitioners should be determining patient exercise ability during all office visits, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q50 Primary care practitioners should be utilizing behavioral counseling strategies directed at increasing physical activity during all office visits, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q51 Primary care practitioners should be providing written prescriptions for physical activity during all office visits, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q52 Primary care practitioners should be referring patients to exercise professionals when they deem it necessary, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q53 The 5 Step EIM Process

The EIM model relies upon the implementation of a 5 step process, by primary care practitioners. This process is intended to be executed at every office visit and takes approximately 3-5 minutes. The steps are as follows.

1. Assess the patient's current activity levels using the Physical Activity Vital Sign (PAVS)

2. Determine the patient's ability to exercise using the Physical Activity Readiness Questionnaire (PAR-Q)

3.Counsel the patient using behavioral counseling strategies and The Exercise Stages of Change questionnaire (ESC-Q)

4. Provide a handwritten prescription for physical activity

5. Provide the patient with a referral to an exercise professional, when necessary

Primary care practitioners should execute all 5 steps of the EIM process at every office visit, it is within their scope of practice.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q59 The 5 Step EIM Process
The EIM model relies upon the implementation of a 5 step process, by primary care practitioners. This process is intended to be executed at every office visit and takes approximately 3-5 minutes. The steps are as follows.
1. Assess the patient's current activity levels using the Physical Activity Vital Sign (PAVS)
2. Determine the patient's ability to exercise using the Physical Activity Readiness Questionnaire (PAR-Q)
3.Counsel the patient using behavioral counseling strategies and The Exercise Stages of Change questionnaire (ESC-Q)
4. Provide a handwritten prescription for physical activity
5. Provide the patient with a referral to an exercise professional, when necessary

I feel that it is possible to effectively execute all 5 steps of the EIM process in 3-5 minutes?

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Q60 I would be more likely to execute all, or some, of the 5 step EIM process, if I were reimbursed through standard medical billing procedures.

1. Strongly agree
2. Agree
3. Somewhat agree
4. Neither agree nor disagree
5. Somewhat disagree
6. Disagree
7. Strongly disagree

Section 5: Attitudes Towards Potential Efficacy

Q58 The 5 Step EIM Process The EIM model relies upon the implementation of a 5 step process, by primary care practitioners. This process is intended to be executed at every office visit and takes approximately 3-5 minutes. The steps are as follows.
1. Assess the patient's current activity levels using the Physical Activity Vital Sign (PAVS)
2. Determine the patient's ability to exercise using the Physical Activity Readiness Questionnaire (PAR-Q)
3.Counsel the patient using behavioral counseling strategies and The Exercise Stages of Change questionnaire (ESC-Q)
4. Provide a handwritten prescription for physical activity
5. Provide the patient with a referral to an exercise professional, when necessary

If all 5 steps of the EIM process were carried out by all primary care practitioners during all office visits, how would the physical activity level of the patient population be affected?

1. Greatly Increase
2. Slightly Increase
3. Neither Increase or Decrease
4. Slightly Decrease
5. Greatly Decrease